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Fighting HIV with Machine Learning and HPC

David Heckerman
Distinguished Scientist
Senior Director of e Science
Microsoft Research

Fighting HIV with Machine Learning and High Performance Computing

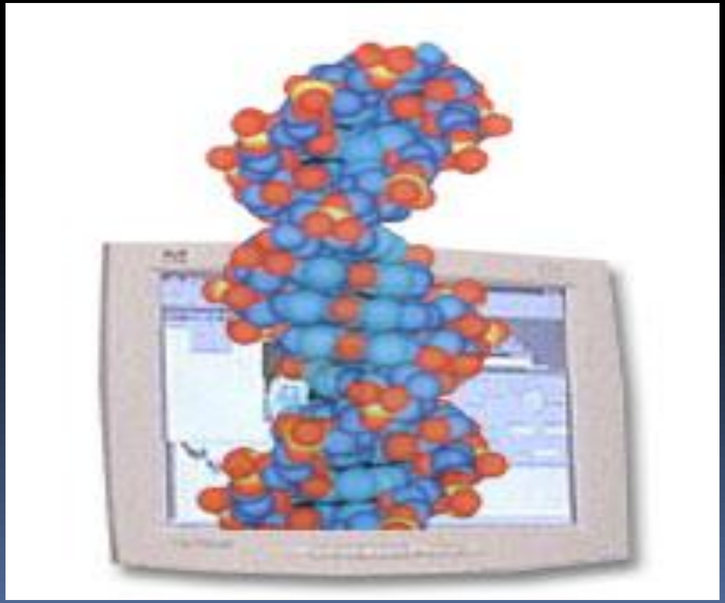
David Heckerman

eScience Group, Microsoft Research

Really? Why?

The convergence of computer science and biology

- DNA is a programming language and a computation device

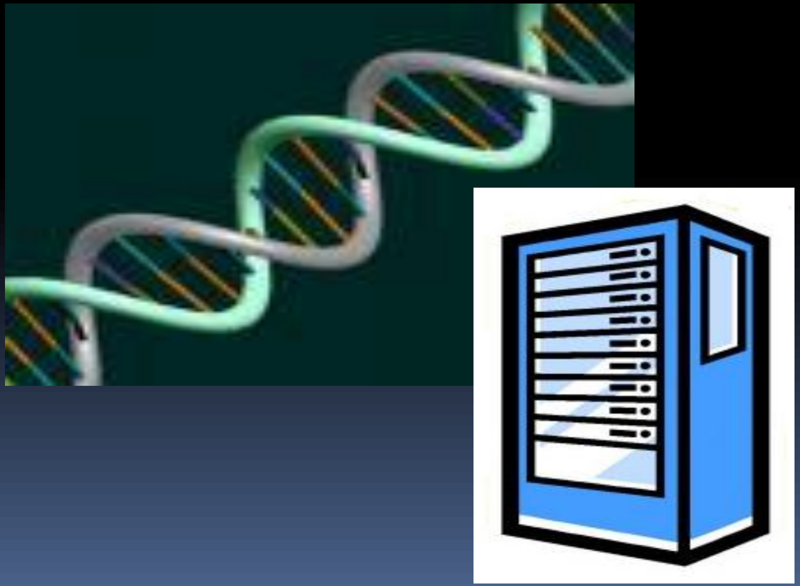


The convergence of computer science and biology

- Drinking from the fire hose or …

The convergence of computer science and biology

- Striking similarities in concepts that can be shared both ways



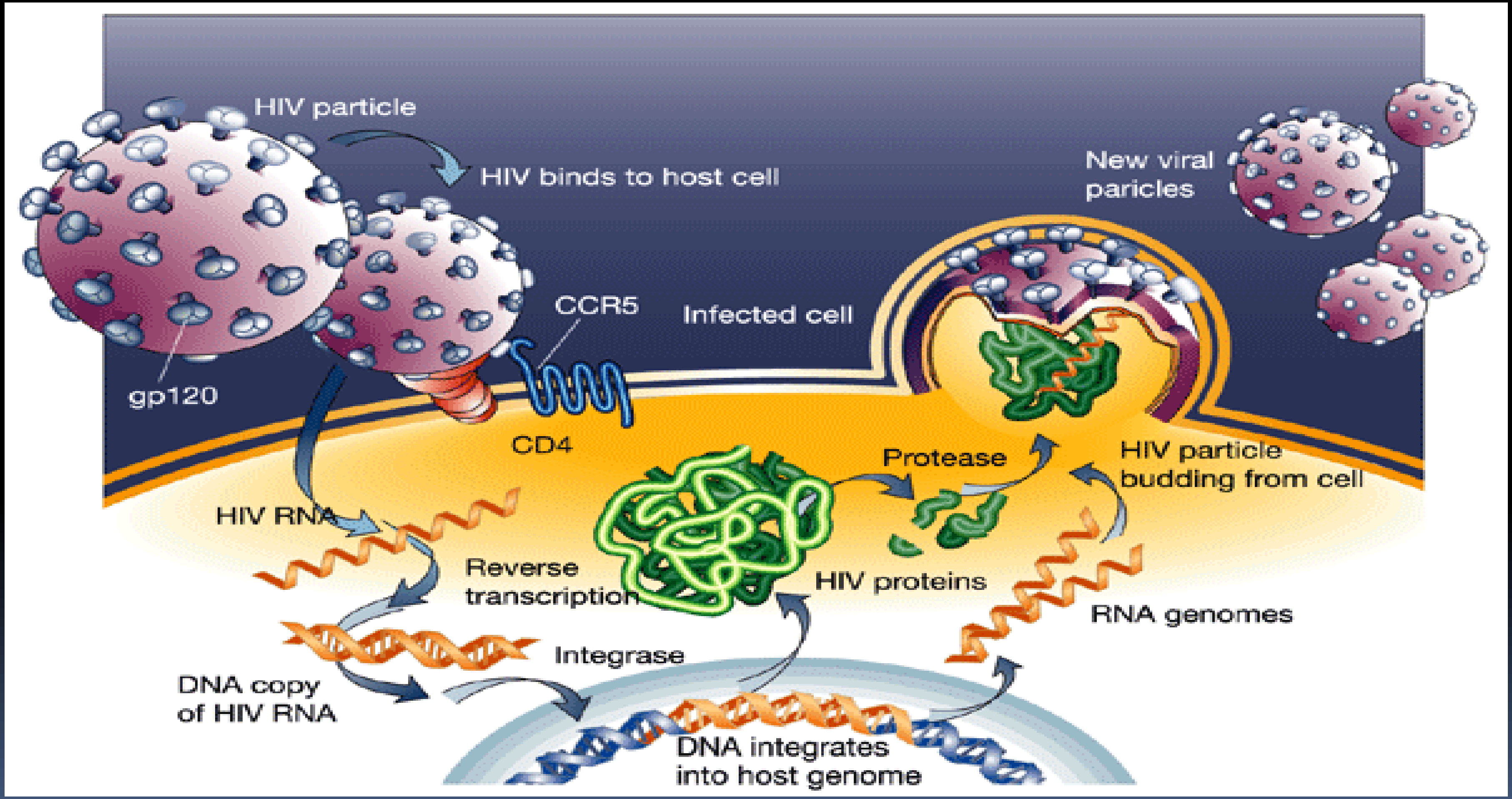
Fighting HIV with machine learning (aka statistics) and high performance computing

- HIV & immunology 101
- PhyloD.net: A tool for studying HIV
- Important discoveries toward a vaccine and possible treatments

HIV is the virus that causes AIDS

- AIDS kills 5,000 people every day
- Drugs work fairly well but are expensive and need to be taken regularly
- Vaccine is perhaps the best hope for developing countries

HIV Lifecycle

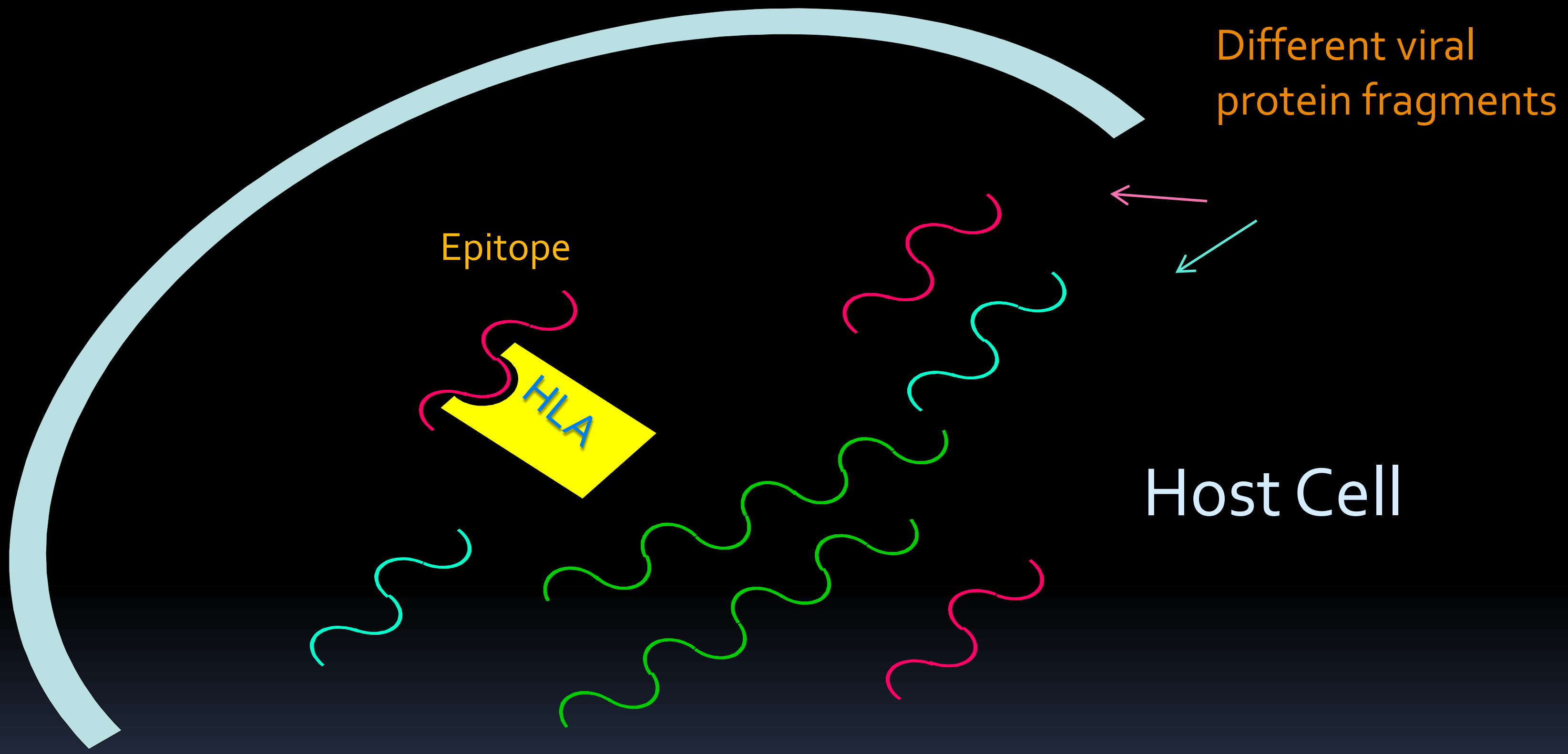


Our immune system fights viral infections

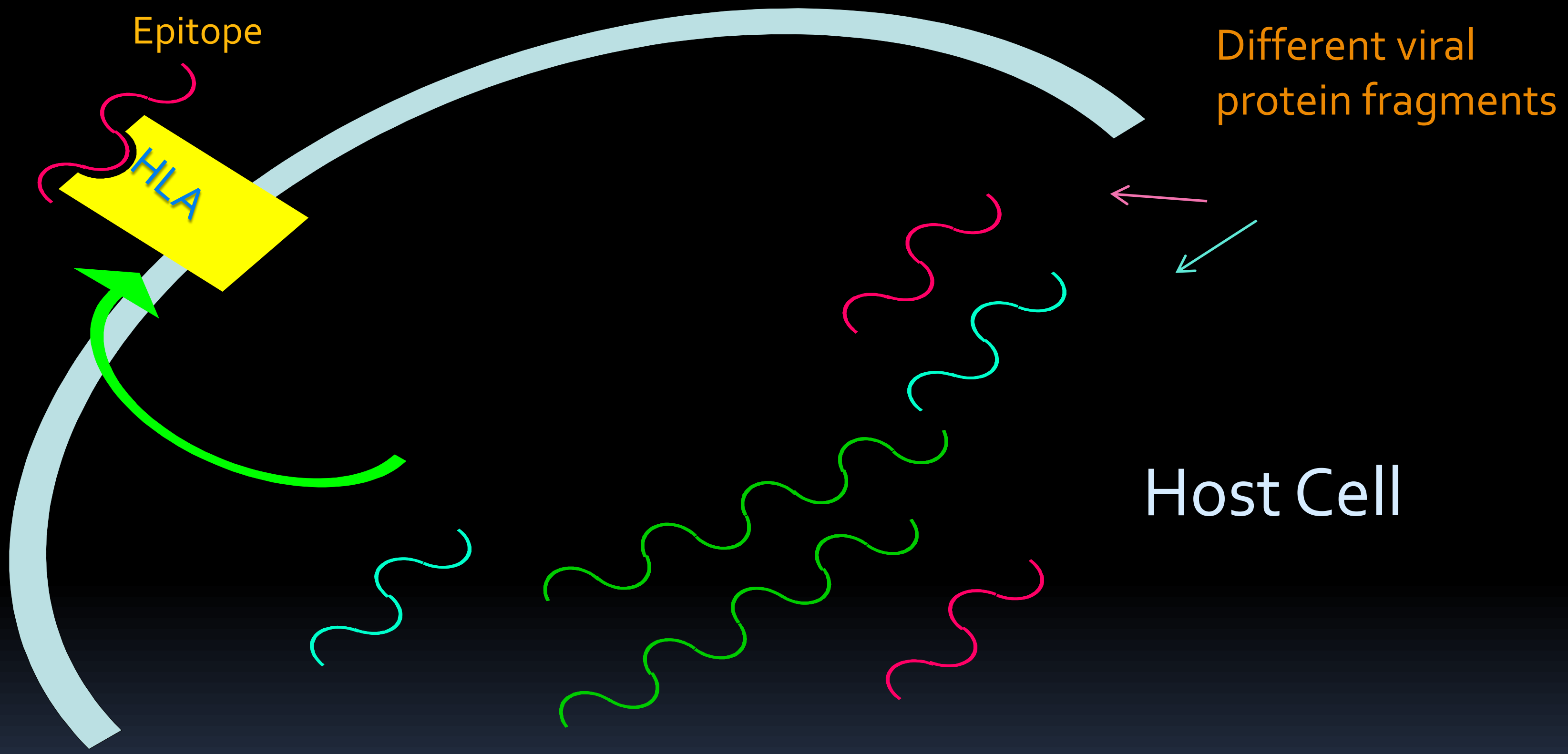
- Innate (e.g., natural killer cells)
- Adaptive
  - Antiboides (humral arm)
  - T cells (cellular arm) ←

Vaccines pretrain the adaptive response thereby generating a stronger response that prevents infection or at least keeps the virus under control

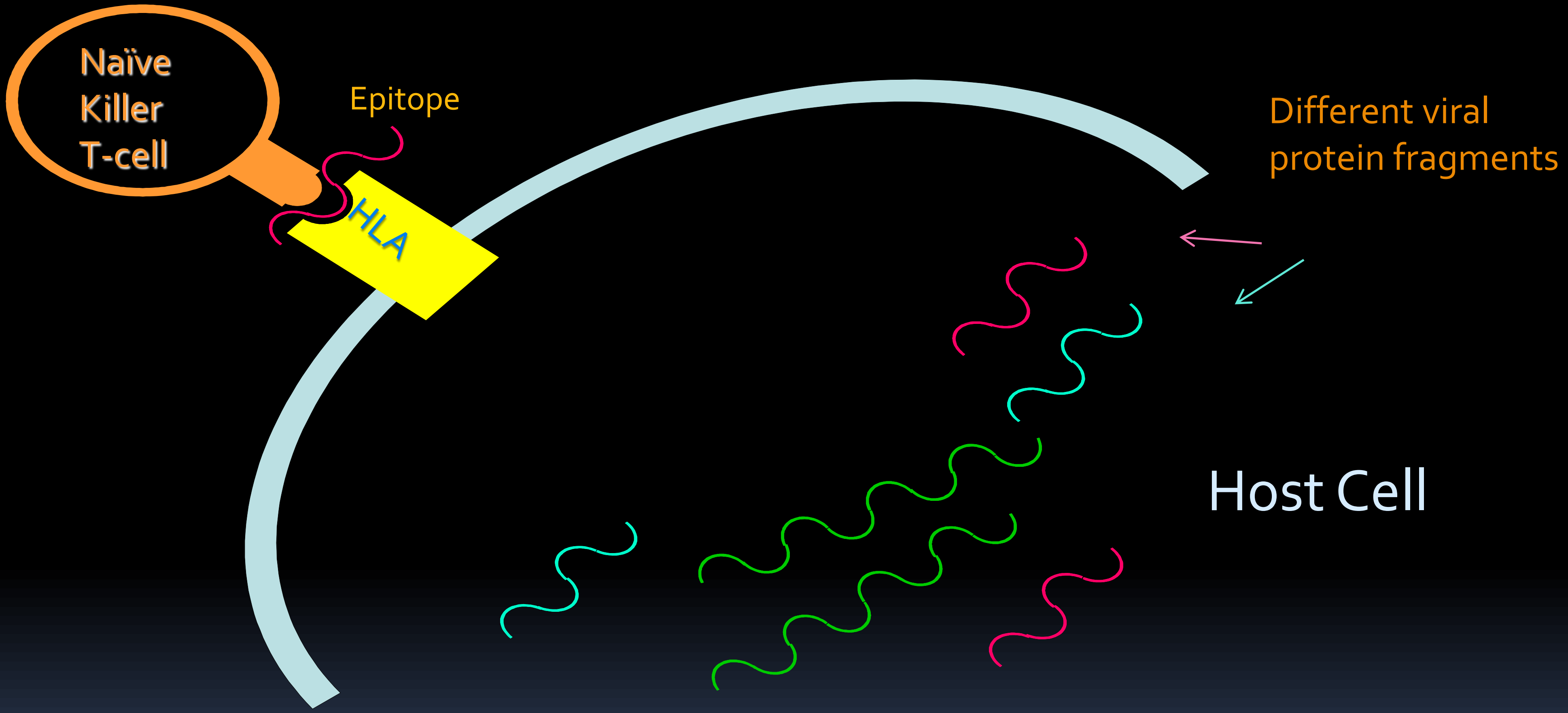
T-cells



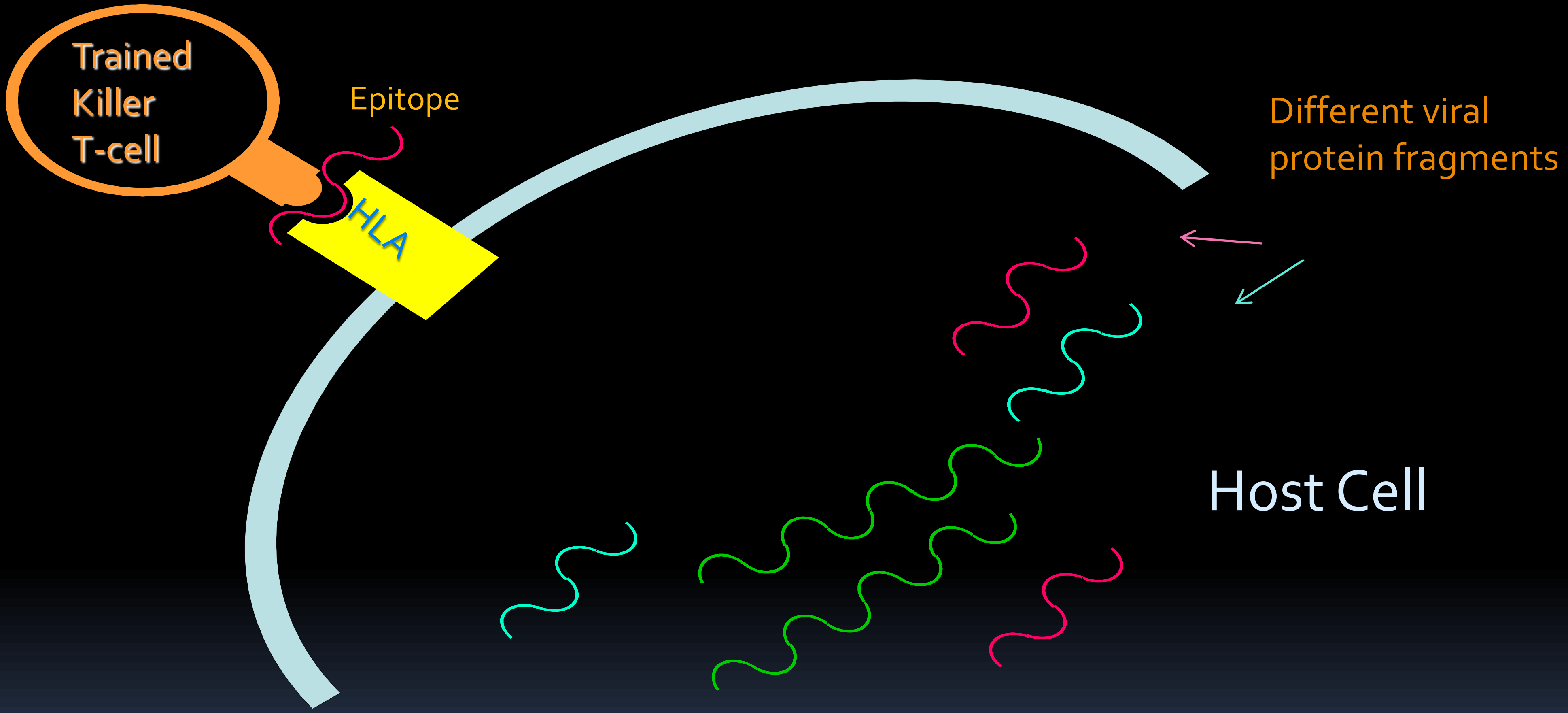
T-cells



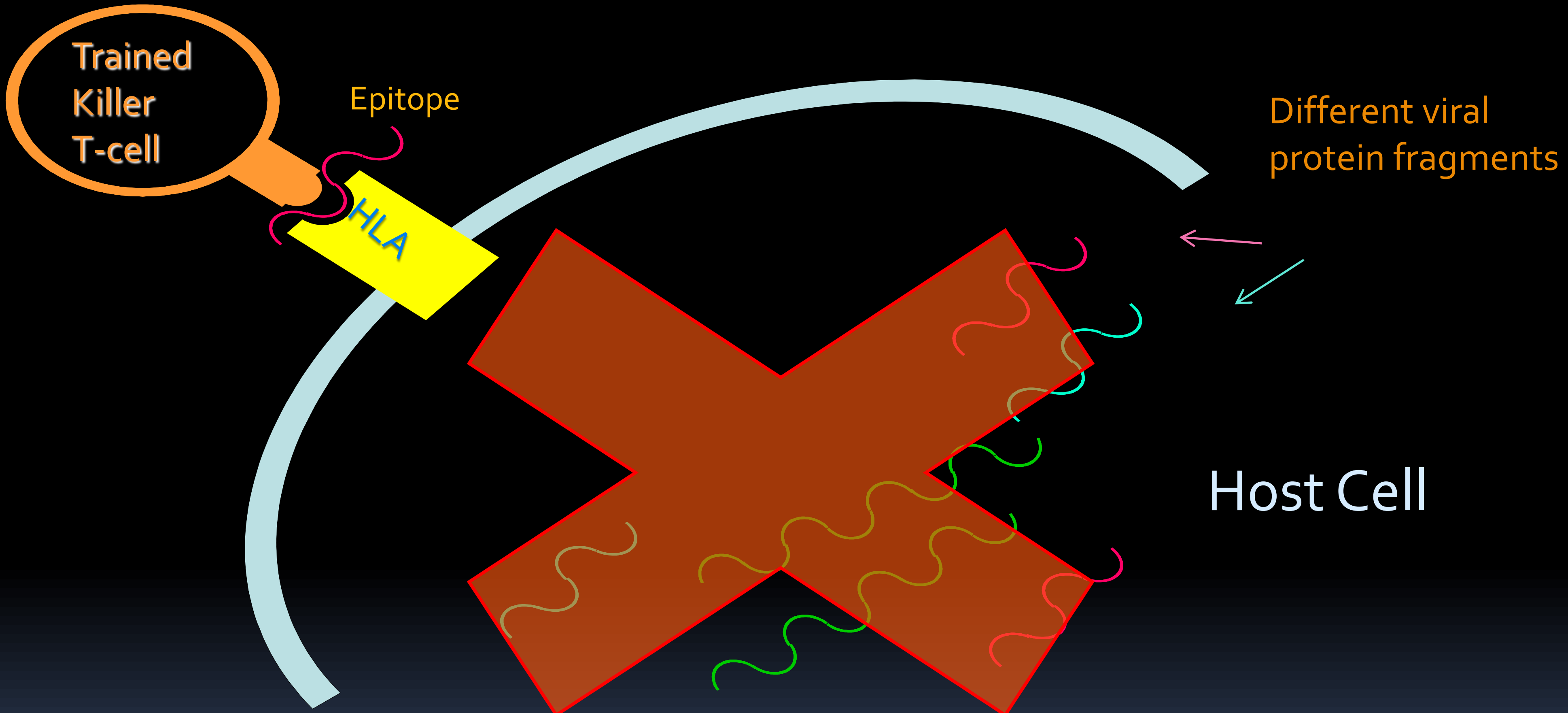
T-cells


Naïve
Killer
T-cell
Epitope
HLA
Different viral
protein fragments
Host Cell

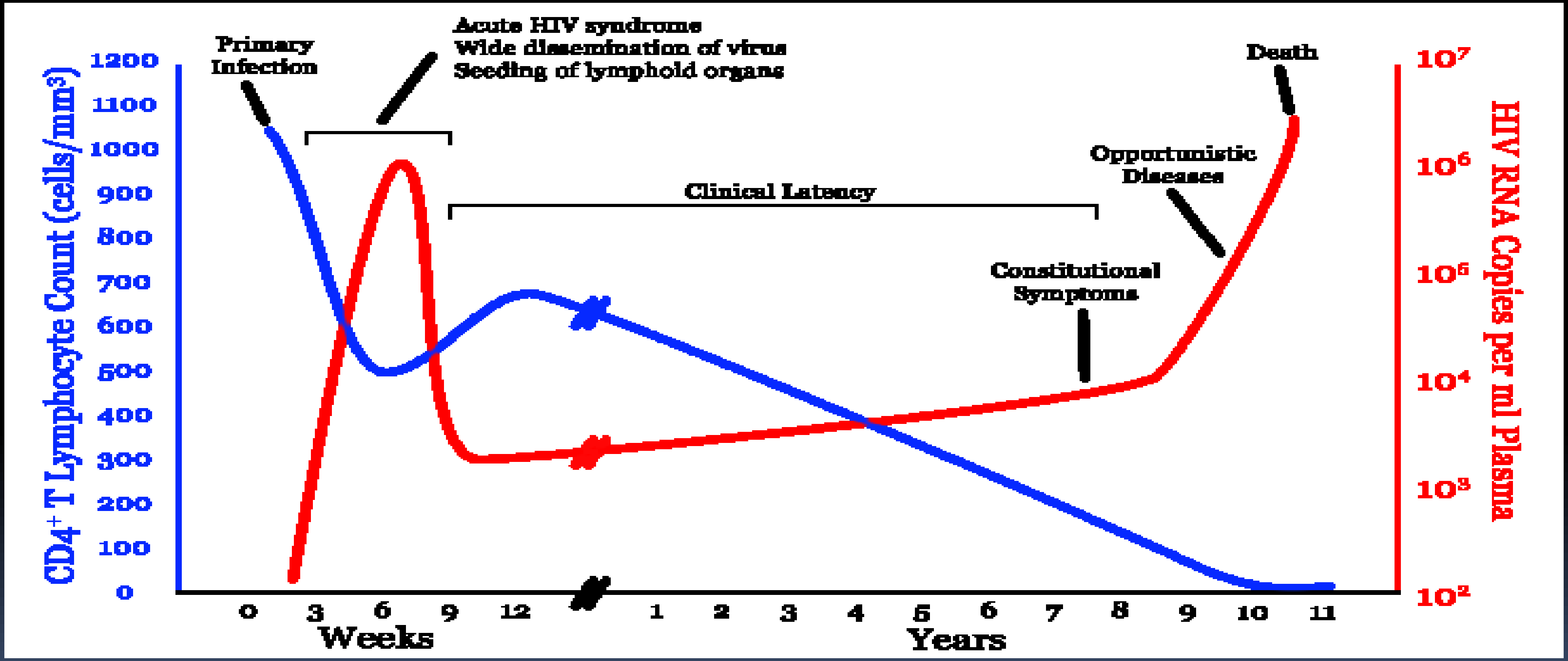
T-cells

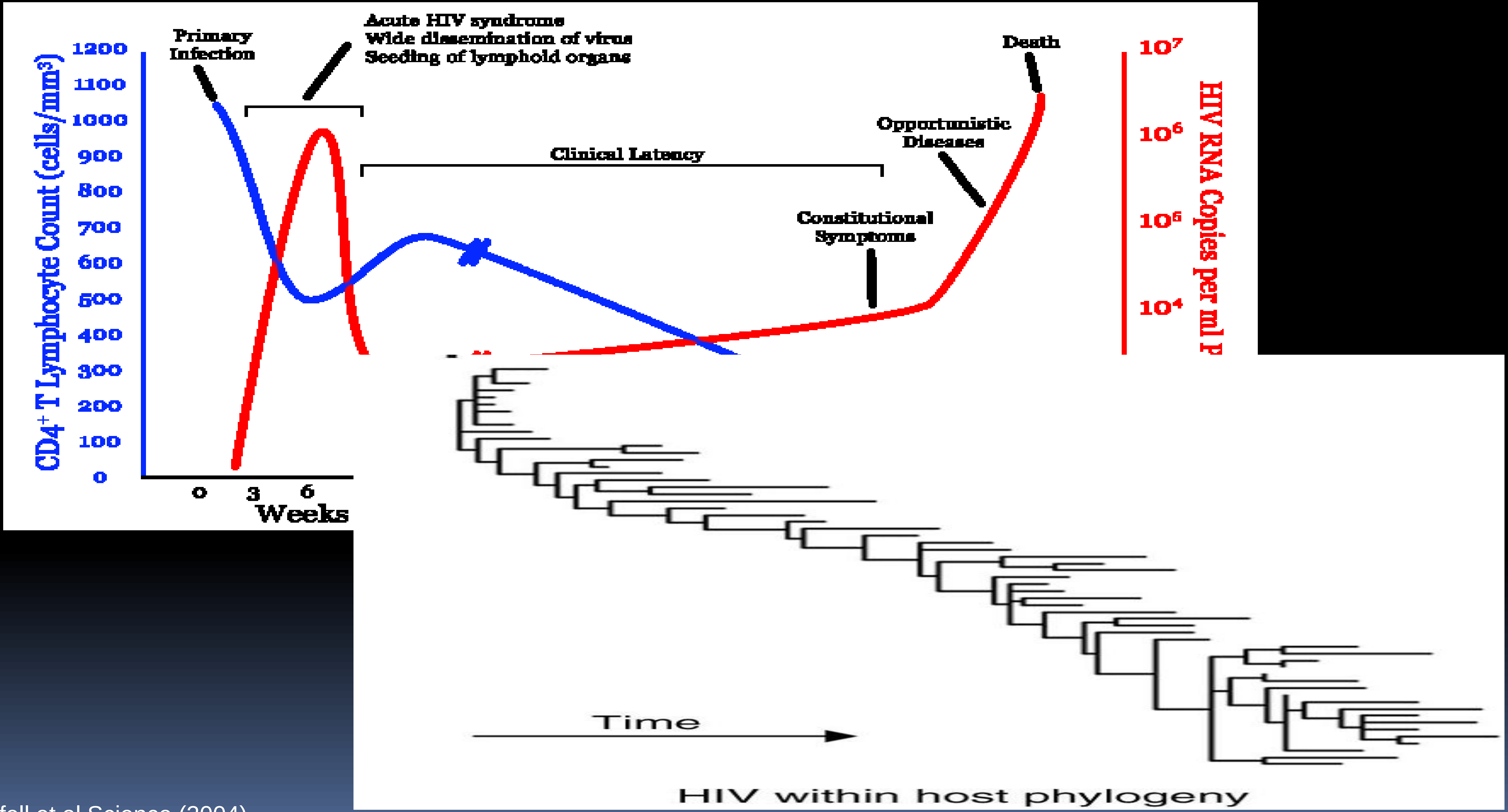

Trained
Killer
T-cell
Epitope
HLA
Different viral
protein fragments
Host Cell

T-cells

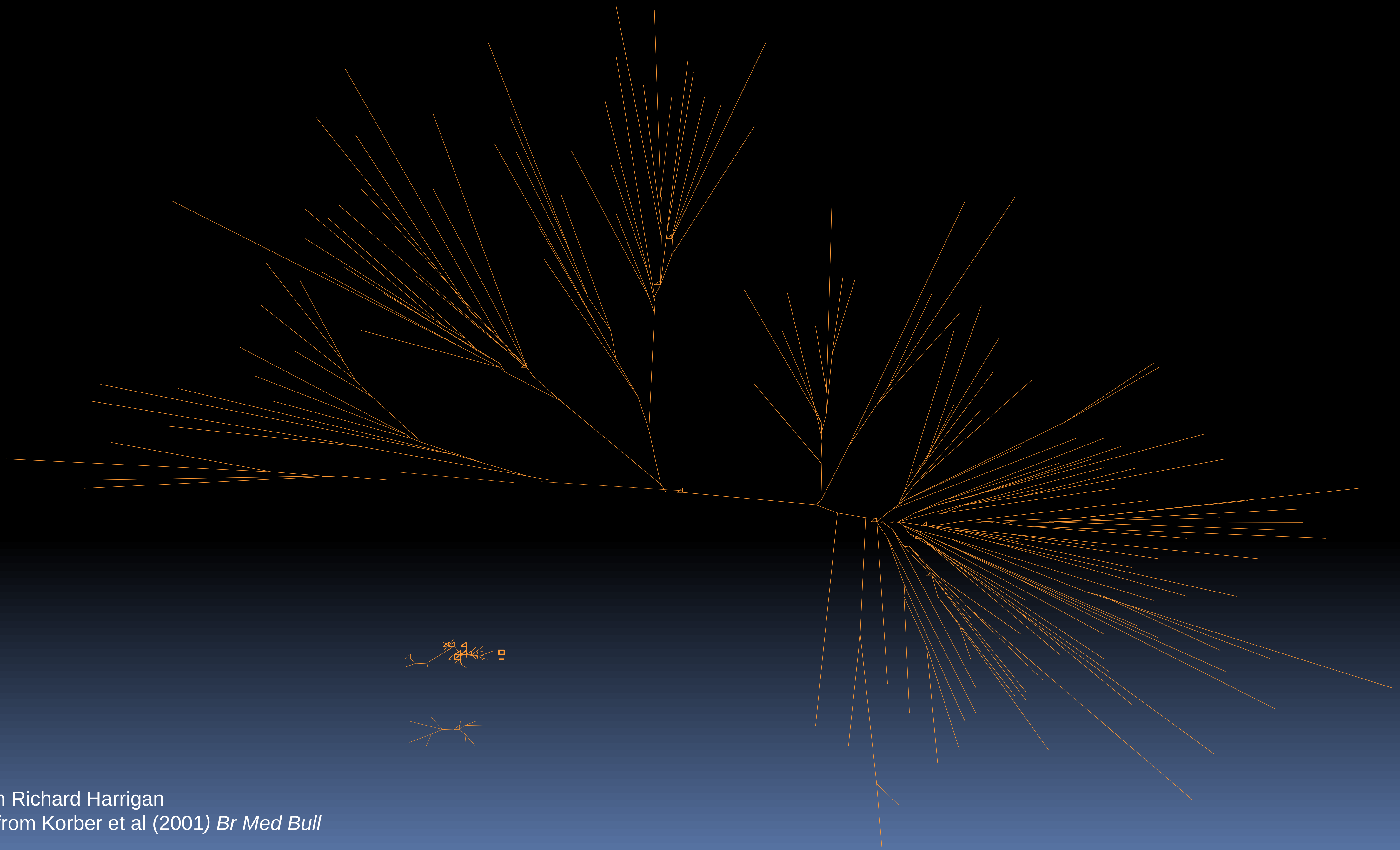

Trained
Killer
T-cell
Epitope
HLA
Different viral
protein fragments
Host Cell

Progression to AIDS



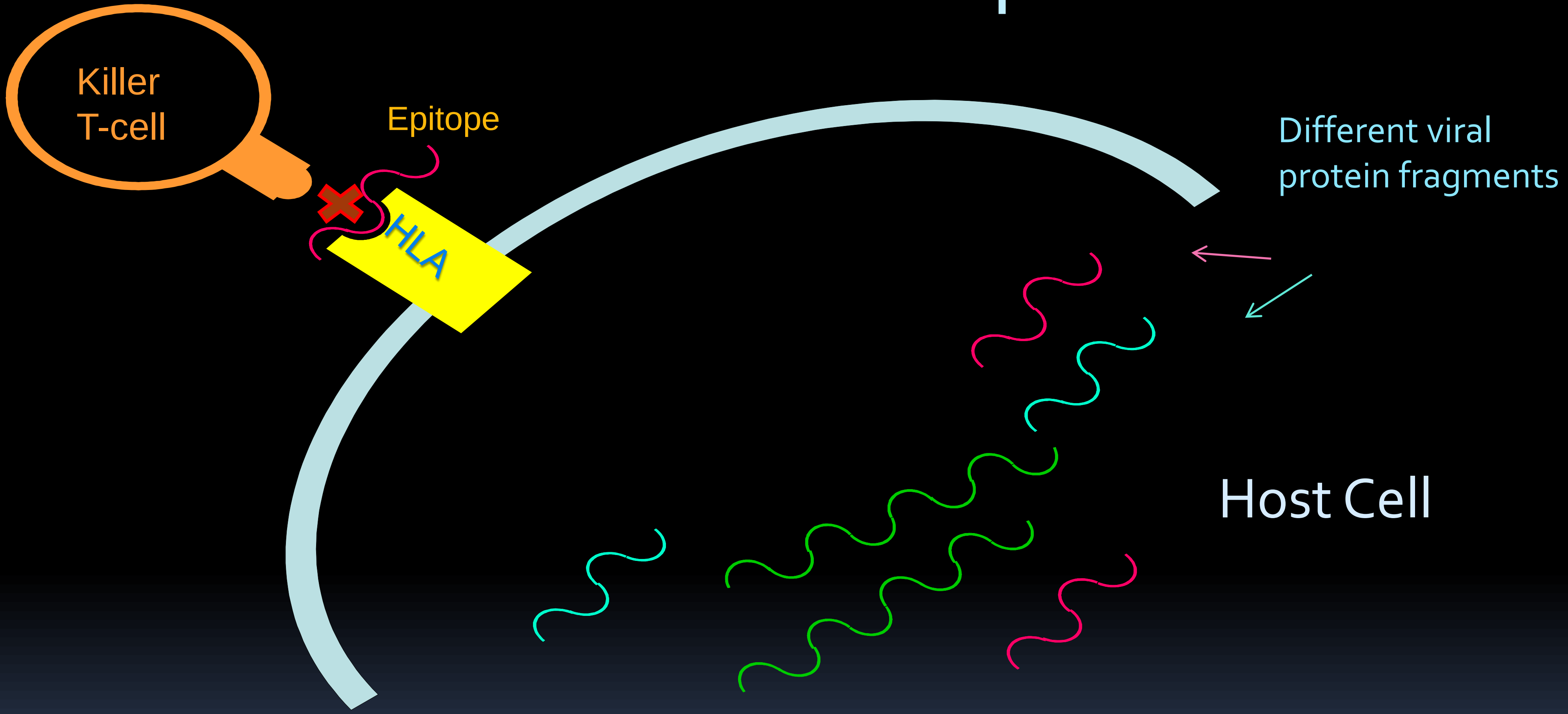


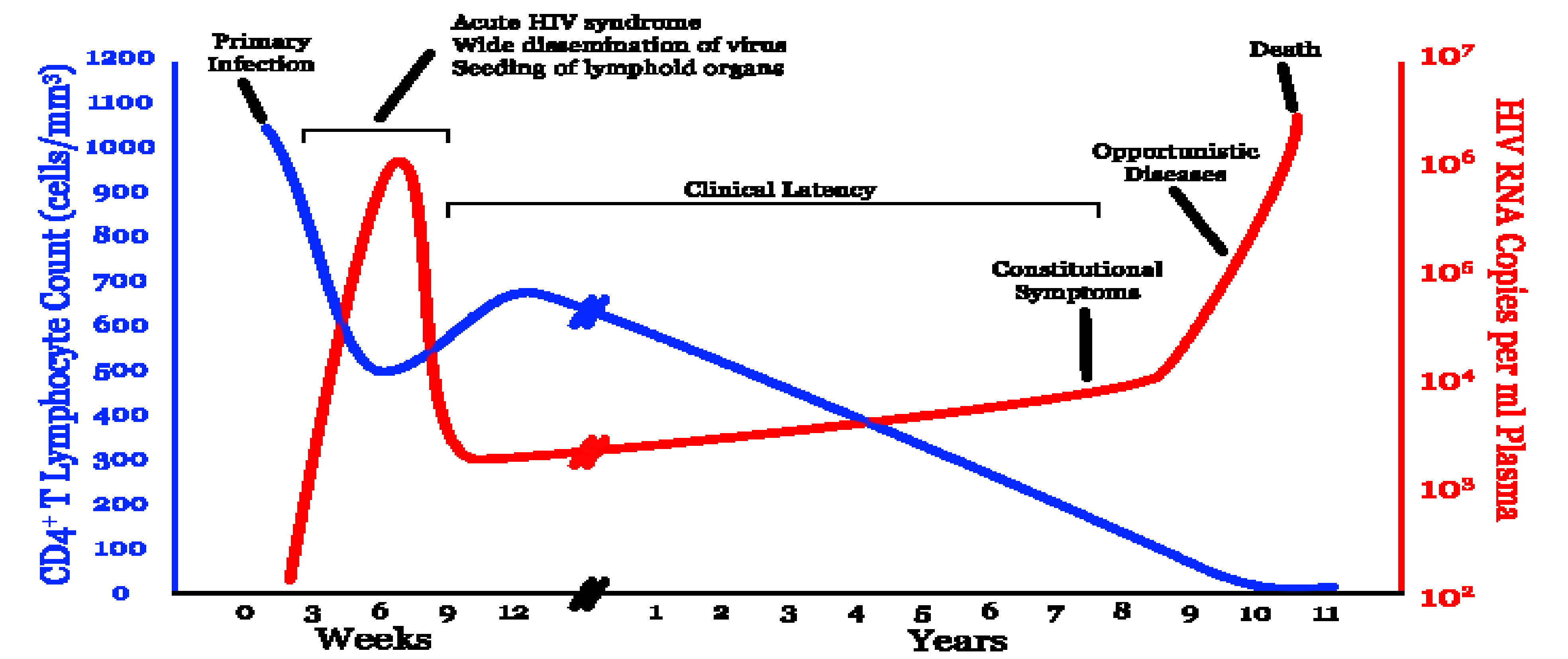
Grenfell et al Science (2004)
Shankarappa et al J Virol (1999)



Slide from Richard Harrigan
Adapted from Korber et al (2001) *Br Med Bull*

Mechanisms of T-cell Escape




Primary Infection
Acute HIV syndrome
Wide dissemination of virus
Seeding of lymphoid organs
Death
Clinical Latency
Opportunistic Diseases
Constitutional Symptoms
CD4+ T Lymphocyte Count (cells/mm3)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
HIV RNA Copies per ml Plasma
10⁷
10⁶
10⁵
10⁴
10³
10²
0
3
6
9
12
Weeks
1
2
3
4
5
6
7
8
9
10
11
Years

Spam filtering

STOPPING SPAM

What can be done to stanch the flood of junk e-mail messages?

By Joshua Goodman, David Heckerman an Robert Rounthwaite

FOR ONE THIRD of all e-mail users, about four out of five incoming messages are spam. Computer scientists today are matched against spammers in an ongoing arms race to control what gets through to your in-box.

In 1978 the first spam e-mail—a plug from a marketing representative at Digital Equipment Corporation for the new DECSystem-20 computer—was dispatched to about 400 people on the Arpanet. Today junk correspondence in the form of unwanted commercial solicitations constitutes more than two thirds of all e-mail transmitted over the Internet, accounting for billions of messages every day. For a third of all e-mail users, about 80 percent of the messages received are spam. Recently spam has become more threatening with the proliferation of so-called phishing attacks—fake e-mails that look like they are from people or institutions you trust but that are actually sent by crooks to steal your credit-card numbers or other personal information. Phishing attacks cost approximately $1.2 billion a year, according to a 2004 Gartner Research study.

The phenomenon of spam afflicts more than just e-mail. Inside chat rooms lurk "robots" that pretend to be human and attempt to convince people to click on links that lead to pornographic Web sites. Instant messaging (IM) users suffer from so-called spIM—e-mail spam cognates. Blogs can be corrupted by "link spammers" who degrade Internet search engine operations by adding misleading links to sites that distort the utility ratings of Web sites and links.

The suffocating effect of spam sometimes seems likely to undermine, if not wreck, Internet communications as we have come to know them. The reality, however, is not so bleak. Several techniques for intercepting spam and discouraging spammers have been invented, and more are on the way. The methods we shall discuss focus on junk e-mail, but many of them could apply to other incarnations of spam as well. No one of these will be a magic cure, but combinations—if embraced by enough of us—could work wonders. It is not unrealistic to hope for a day when our e-mail boxes will once again be nearly spam free.

Insidious E-mails

THE PROLIFERATION of fraudulent e-mail results directly from favorable market forces: spam is exceedingly cheap to distribute. It is not altogether free, though. We estimate that a message costs about one hundredth of a cent to send. At these cut-rate prices a spammer can earn only $11 per sale and still make a profit, even if the response rate is as low as one in 100,000. Hence, although very few e-mail users ever buy anything advertised in spam, all of us suffer because of those who do.

One of the most infuriating aspects of spam is that it changes continually to adapt to new attempts to stop it. Each time software engineers attack spam in some way, spammers find a way around their methods. This spam arms race has led to a continuous coevolution of the two, which has resulted in ever increasing sophistication on both sides.

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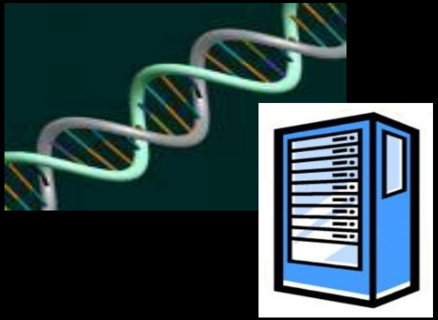
www.sciam.com SCIENTIFIC AMERICAN 43

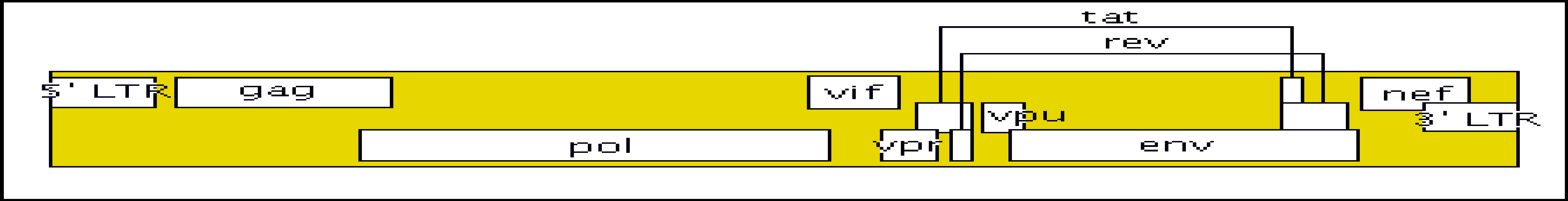
Goodman, Heckerman, & Rounthwaite
Scientific American, April 2005



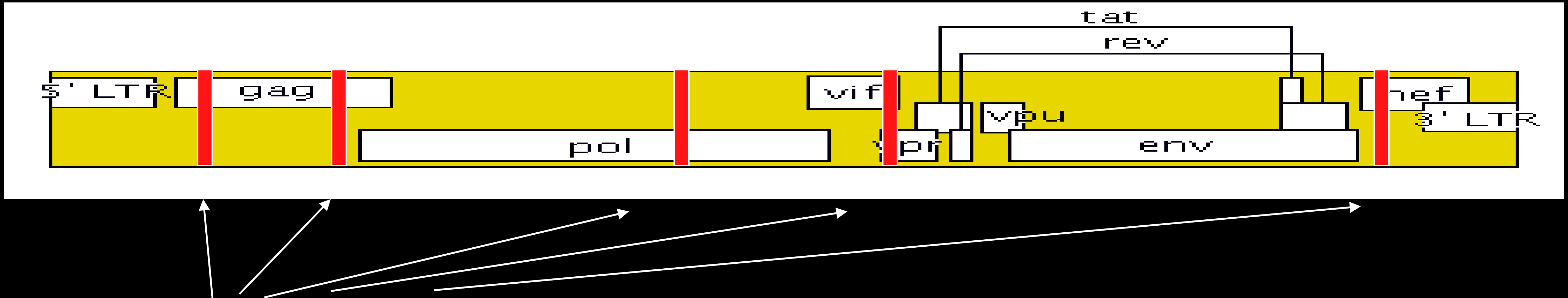
From spam filters to vaccine design

- Immune system attacks HIV: filter blocks spam
- Problem: Spammers "mutate" their emails
- Solution: Spam mail can't be arbitrary – they are trying to sell you something
    - Look for disguised prodcut name (e.g., "V1AGRA")
    - Follow the money

- What is HIV's Achilles' heel?


tat
rev
5' LTR
gag
vif
nef
vpu
3' LTR
pol
vpr
env

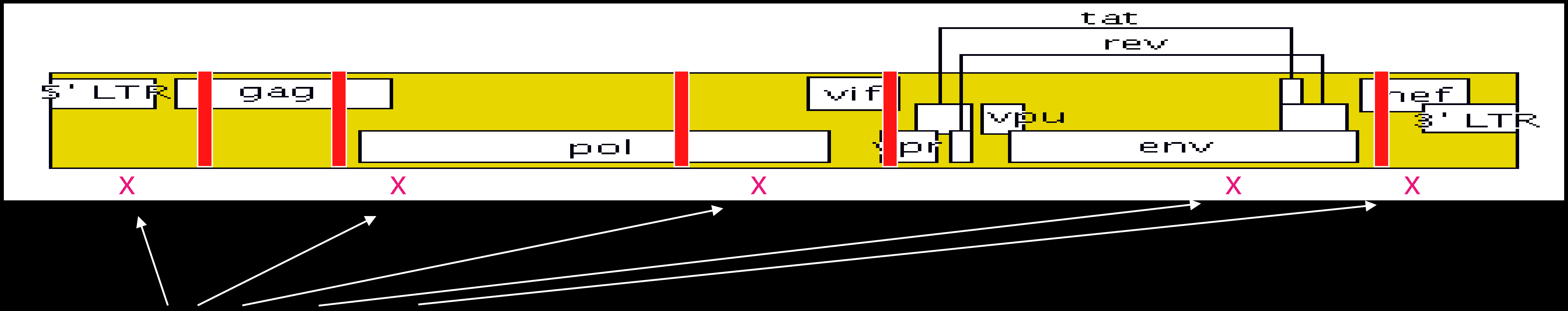
Hypothesis: Certain parts of HIV are critical to its function



If HIV mutates within these epitopes, it becomes less or non-functional

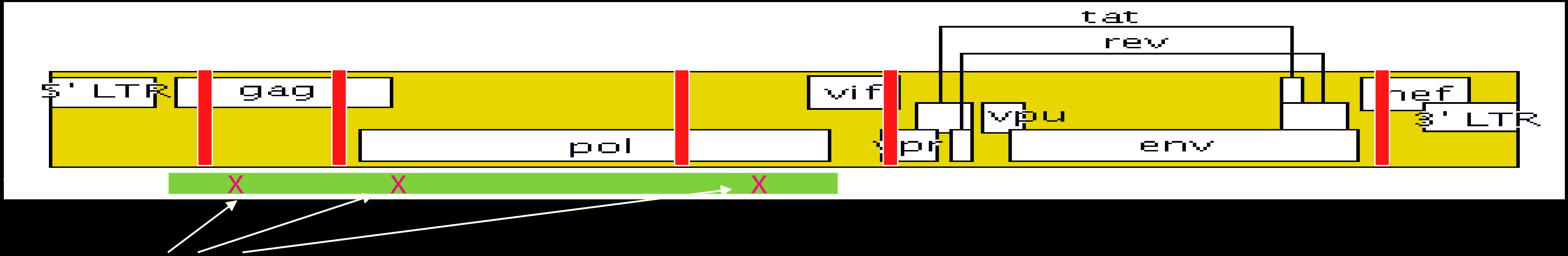
Suggests a vaccine design…

A design for an HIV vaccine



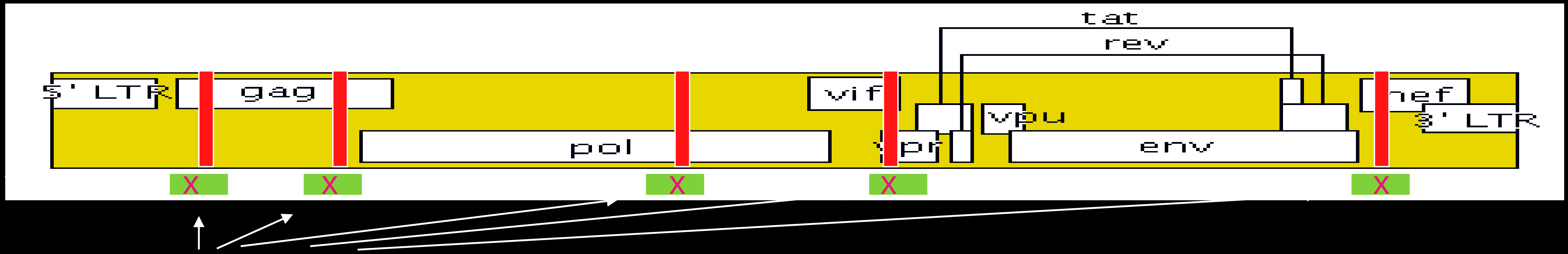
Left to its own devices, our immune system attacks at random epitopes

A design for an HIV vaccine



A “whole protein” vaccine does little to help the situation (explains failure of Merck vaccine)

A design for an HIV vaccine



A focused vaccine can show immune system where to attack

A design for an HIV vaccine

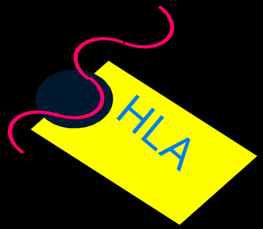
- Accumulating evidence for hypothesis and identifying these "protective epitopes"
  - Brute force testing of known epitiopes (Walker and Pereyra)

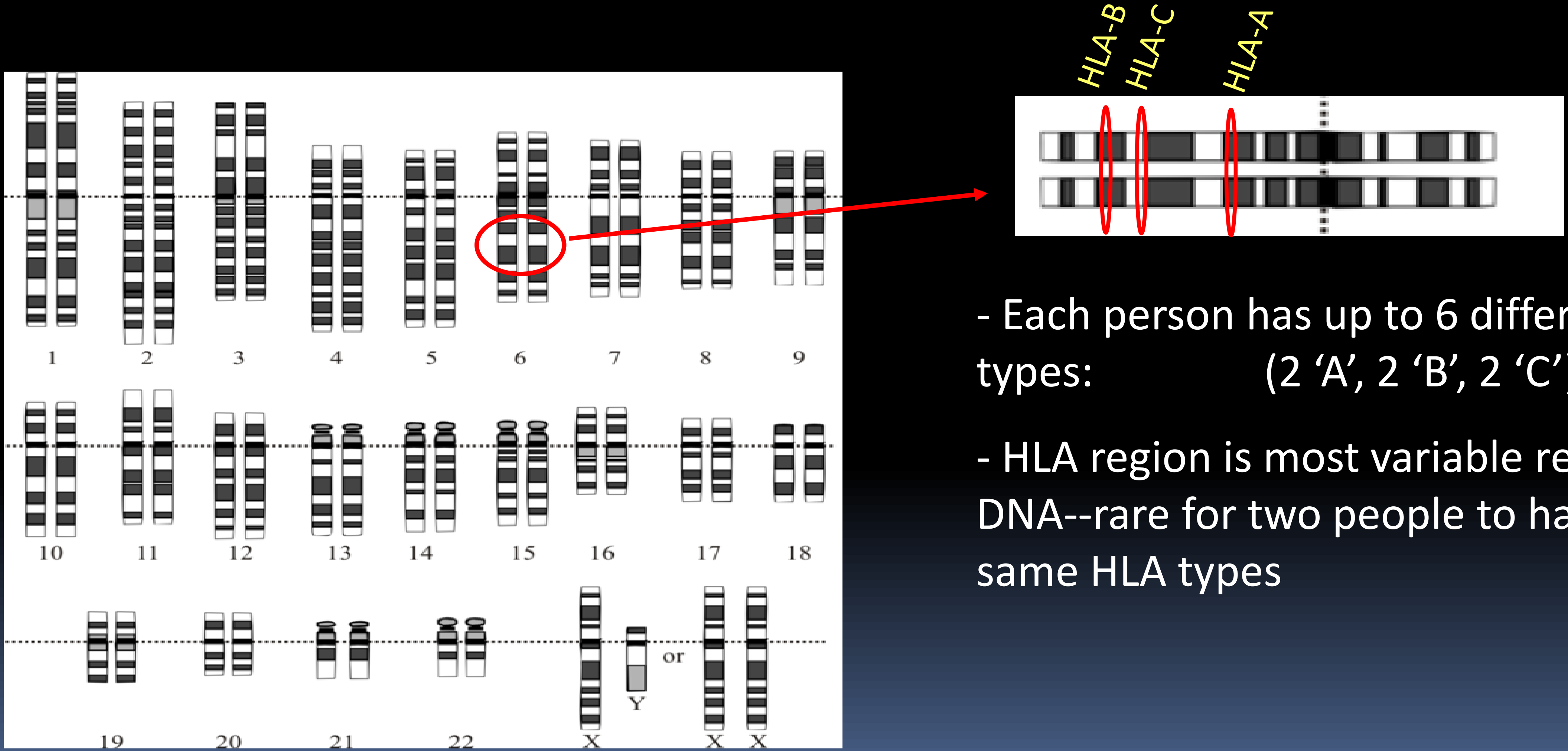
- Continuing to search for these protective epitopes with more clever methods

Fighting HIV with machine learning (aka statistics) and high performance computing

- HIV & immunology 101
- PhyloD.net: A tool for studying HIV
- Important discoveries toward cures/vaccines

HLA variability

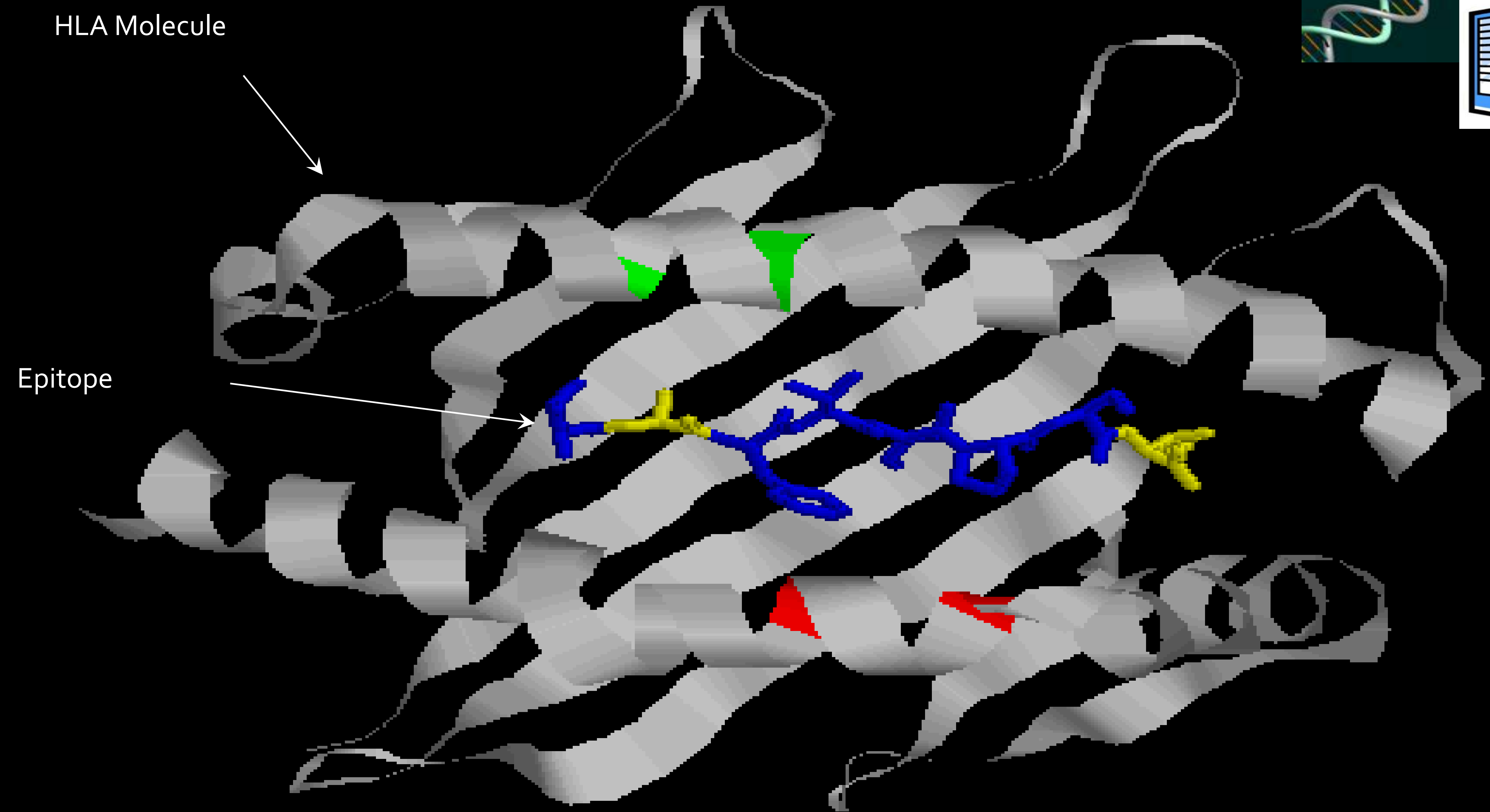




- Each person has up to 6 different HLA types: (2 ‘A’, 2 ‘B’, 2 ‘C’)

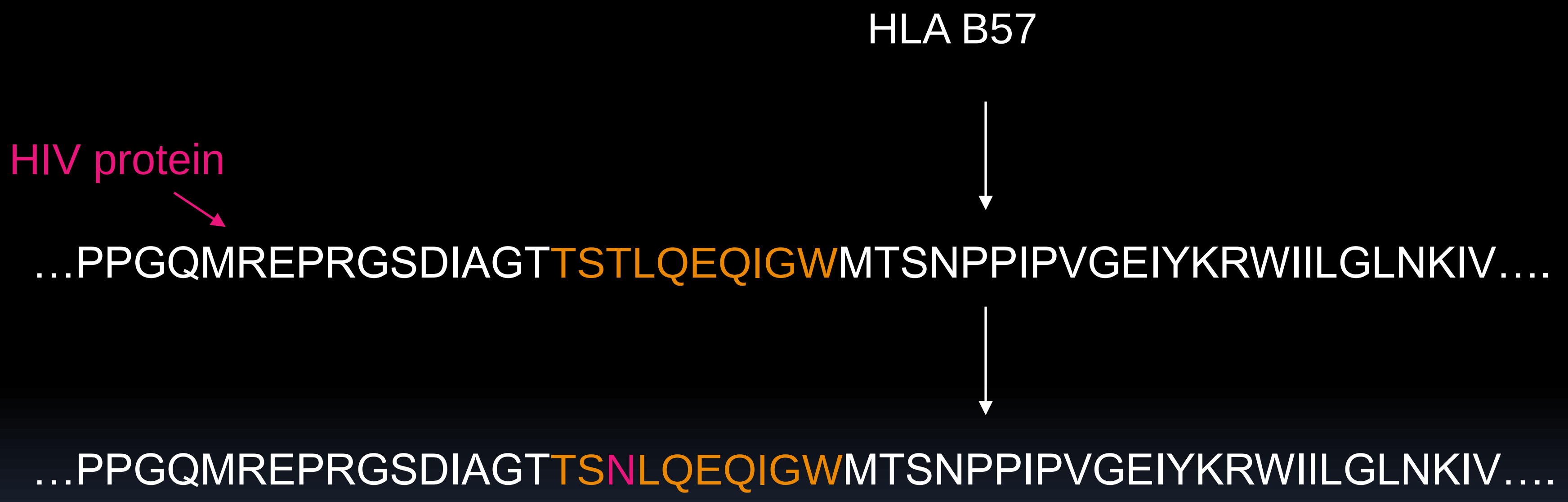
- HLA region is most variable region of DNA--rare for two people to have the same HLA types

Epitope variability



Use this variability to search for epitopes and the HLAs that attack them

Example:



HLA B57

HIV protein

…PPGQMREPRGSDIAGTTSTLQEQIGWMTSNPPIPVGEIYKRWIILGLNKIV….

…PPGQMREPRGSDIAGTTSNLQEQIGWMTSNPPIPVGEIYKRWIILGLNKIV….

Straightforward approach

- Sequence someone’s HIV when they first get infected and re-sequence every month or so

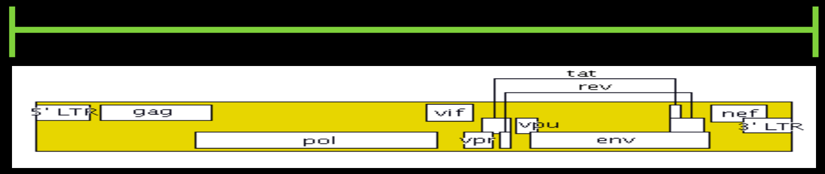
- Expensive, difficult to find subjects early infection (lucky to find 100 in a year)

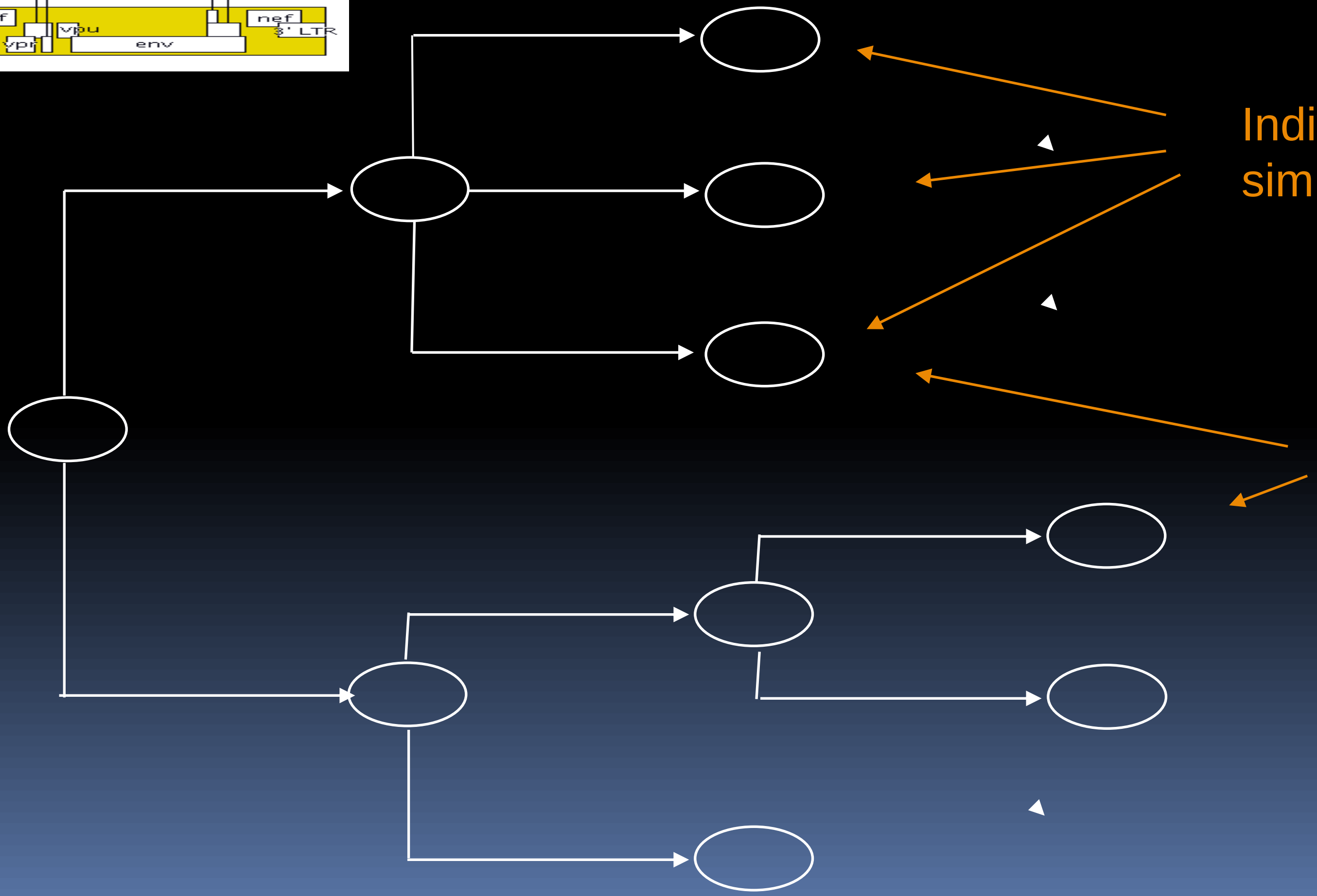
Our approach: PhyloD.net

- Take a single snapshot of a person’s HIV
- Use the phylogeny of sequences among individuals to infer the infecting sequence
- Requires machine learning algorithms and high-performance computing
- Bottom line: much less expensive and can get data from thousands of subjects

PhyloD.Net: Basic idea

Phylogeny of HIV
sequences



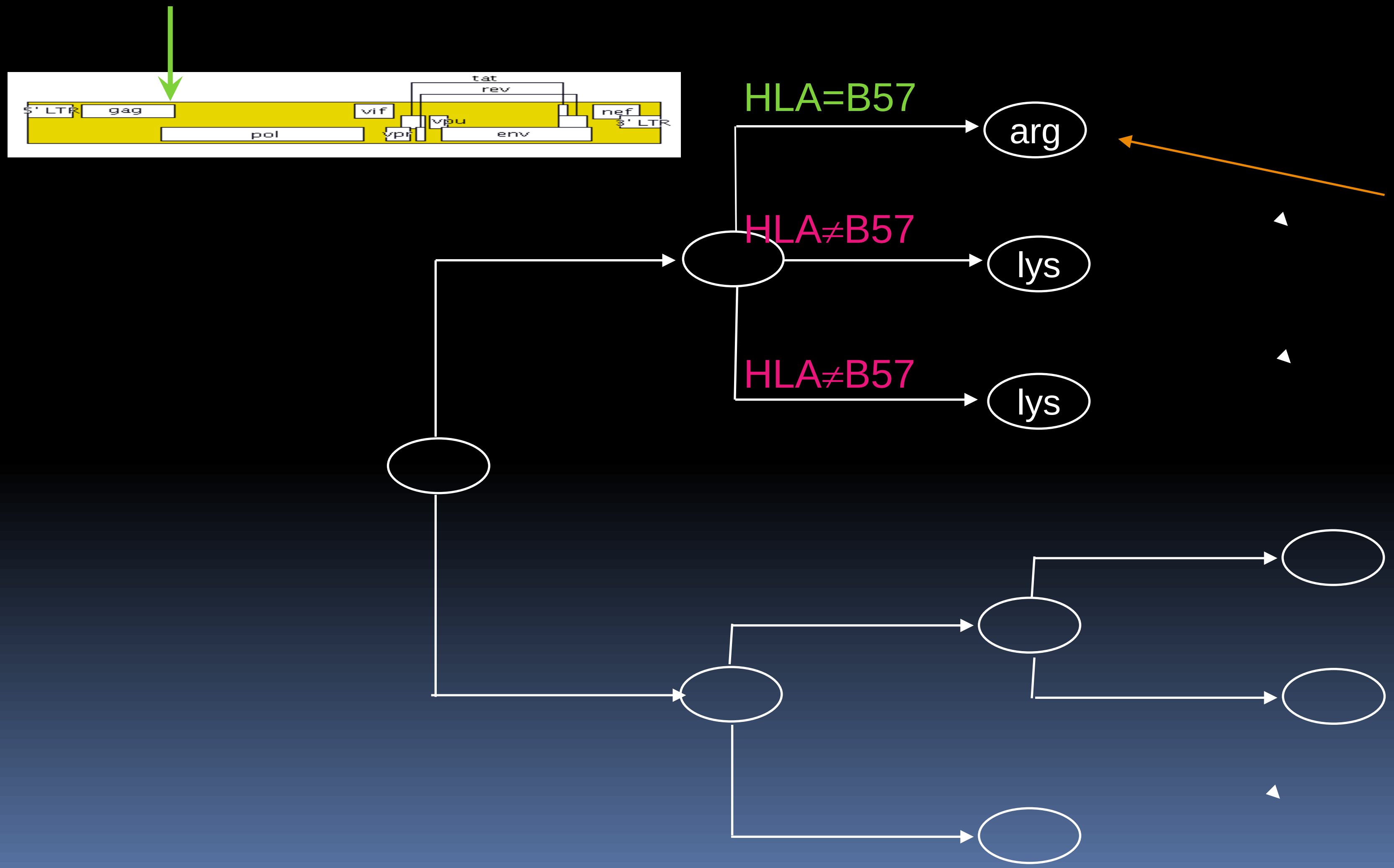


Individuals with
similar sequences

Individuals with not so
similar sequences

PhyloD.Net: Basic idea

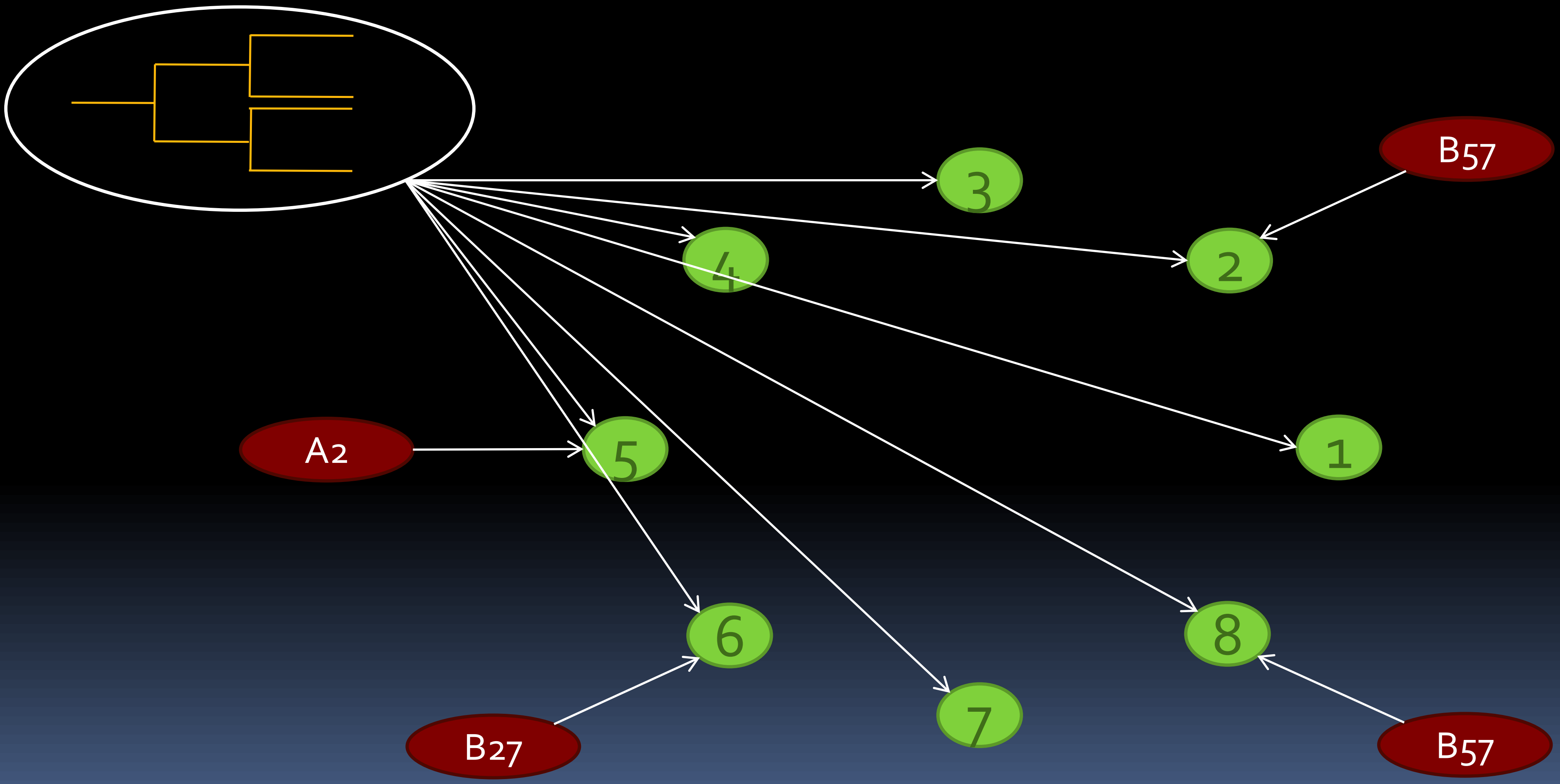
Focus on single position



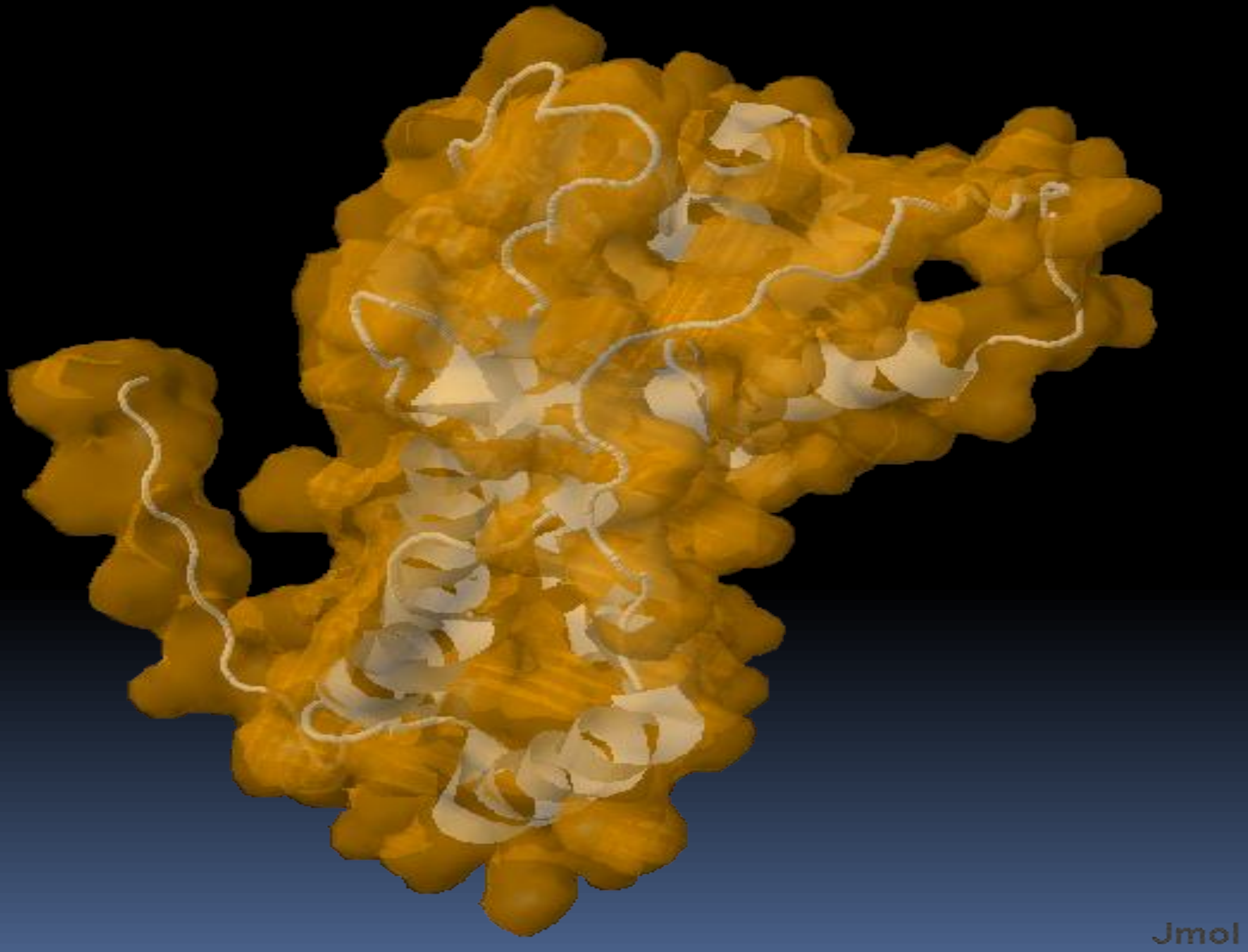
Likely that this individual was infected with lys, which then mutated to arg due to HLA=B57

Multiple positions, multiple HLAs

Science 2007

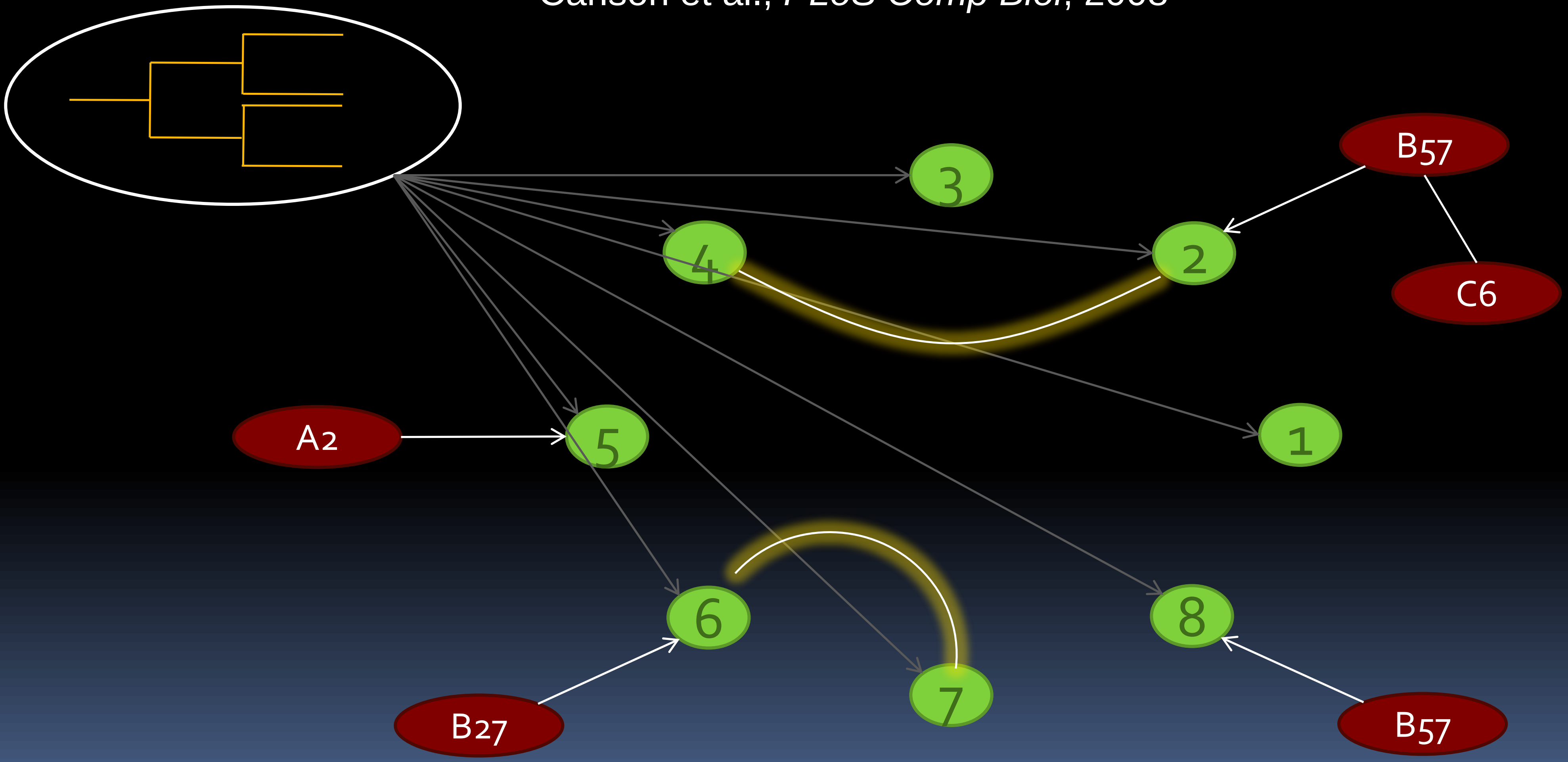


Mutations are not independent



Covariation Effects

Carlson et al., *PLoS Comp Biol*, 2008



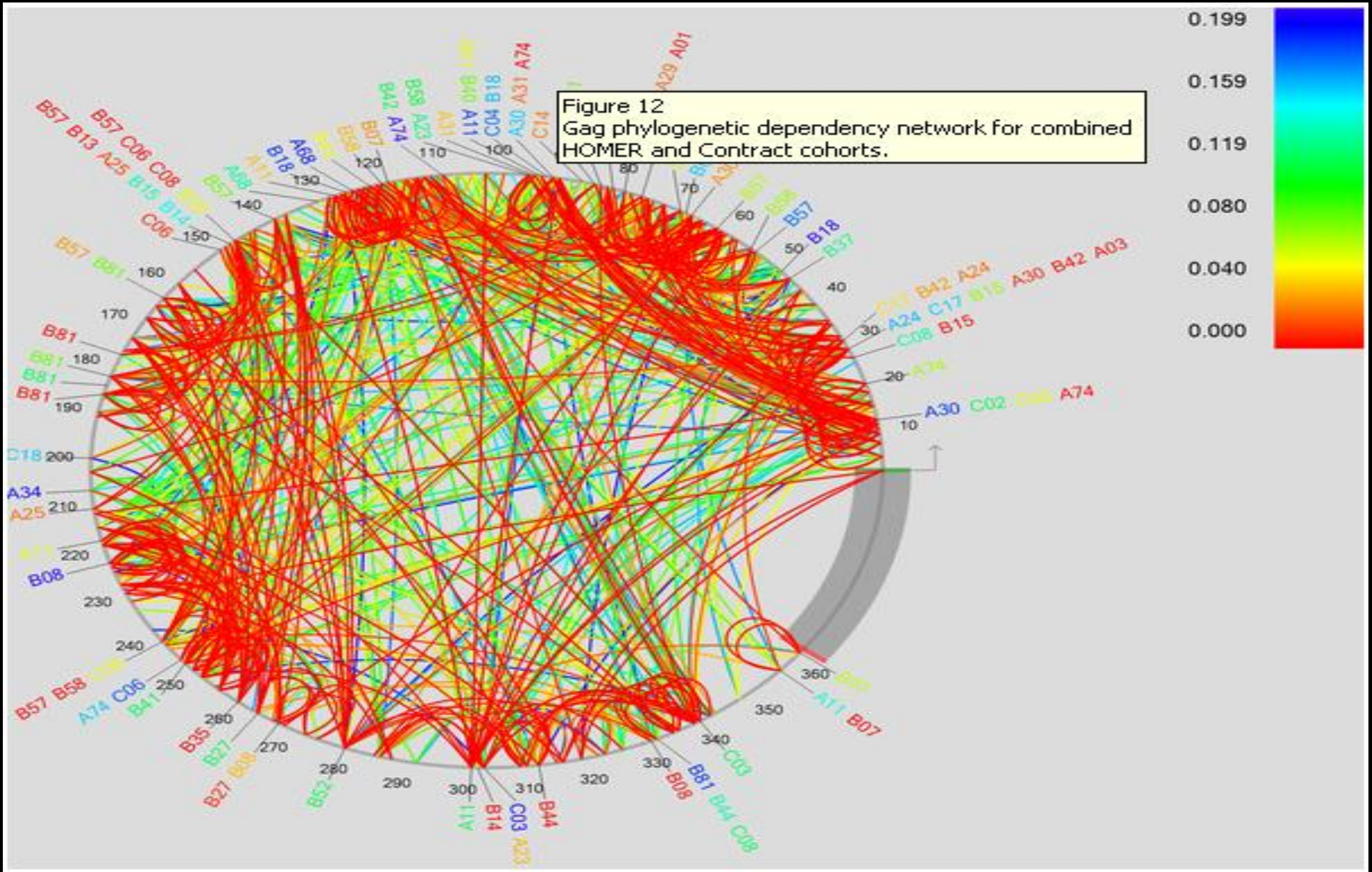
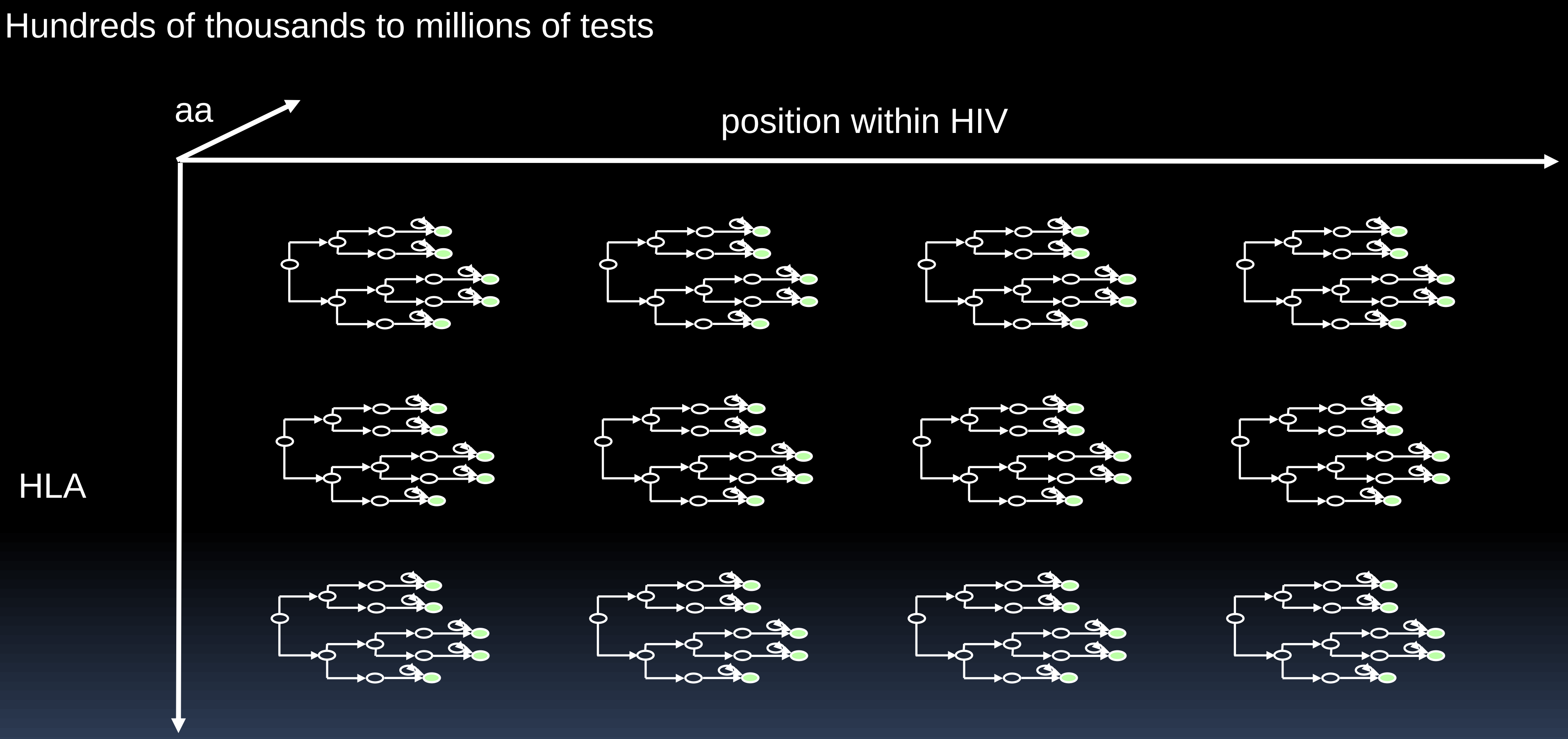


Figure 12
Gag phylogenetic dependency network for combined HOMER and Contract cohorts.

PhyloD on cover of *PLoS Comp Bio*, Nov 2008

High performance computing a must



Fortunately, the computations are pleasantly parallel

Fighting HIV with machine learning (aka statistics) and high performance computing

- HIV & immunology 101
- PhyloD.net: A tool for studying HIV
- Important discoveries toward cures/vaccines

PhyloD.net publications

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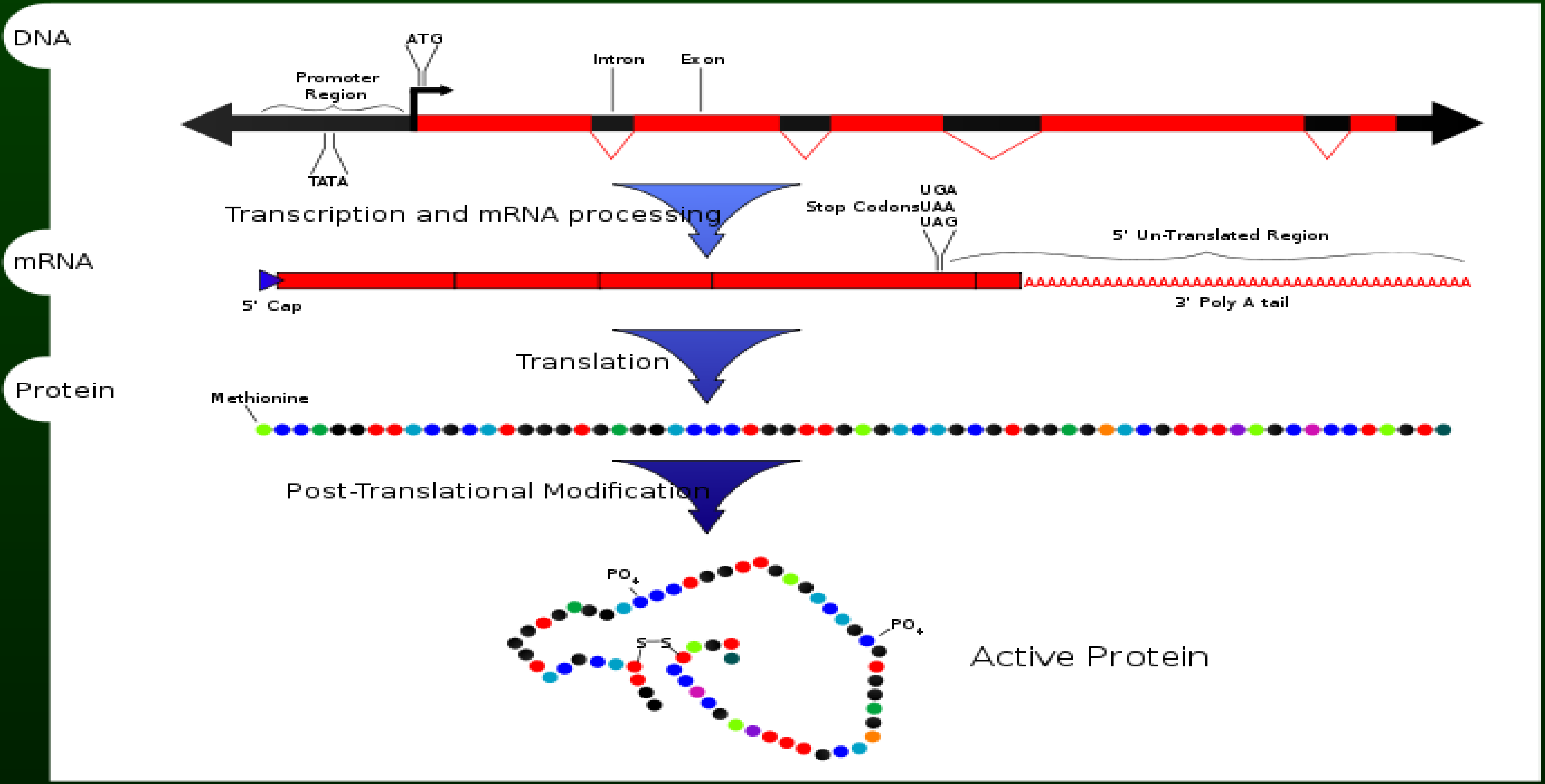
Nature

Science

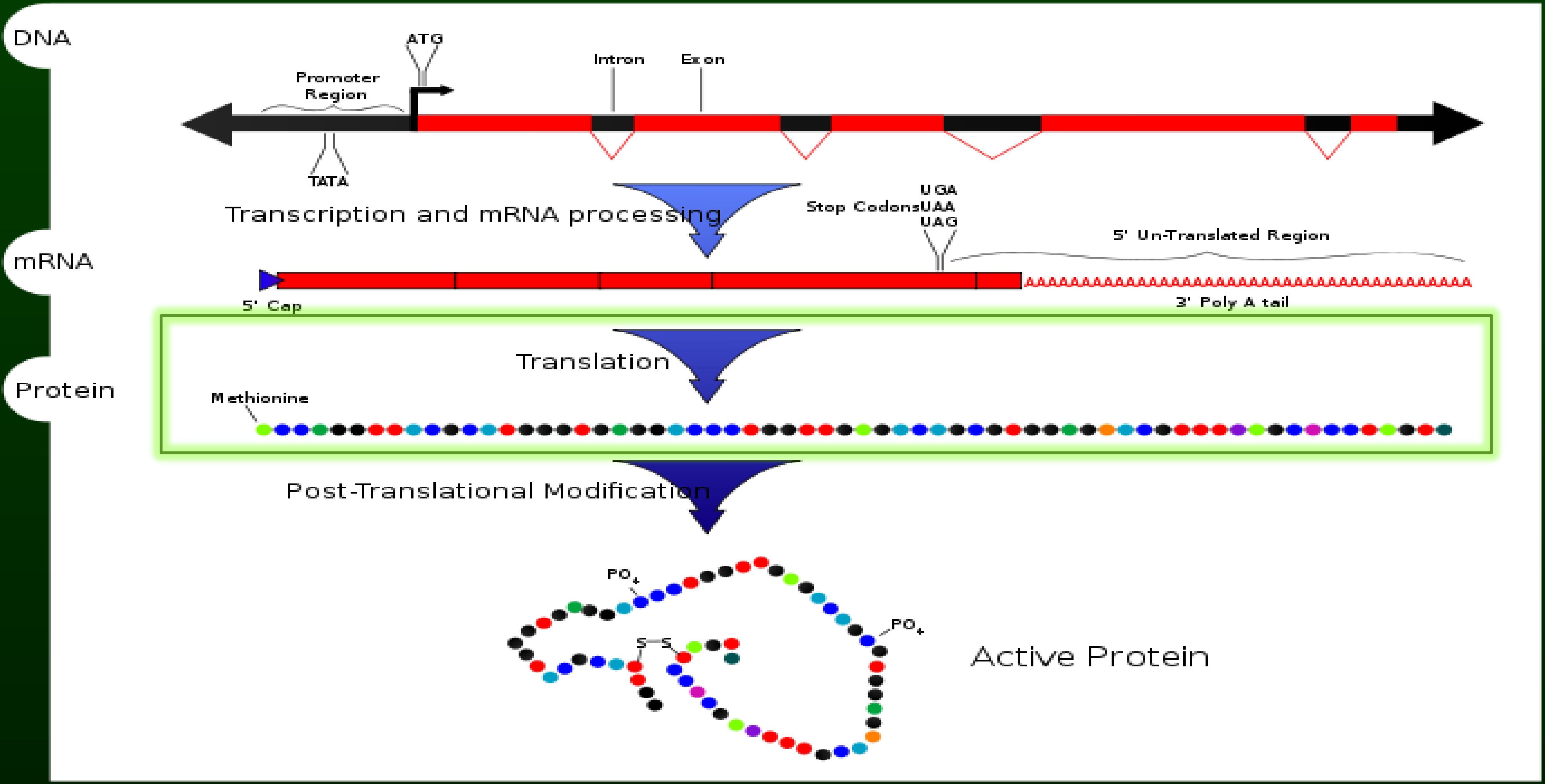
What do they tell us?

- Identifying more normal epitopes (11)
- Identifying novel class of epitope targets (2)
- Identifying novel immune responses (1)

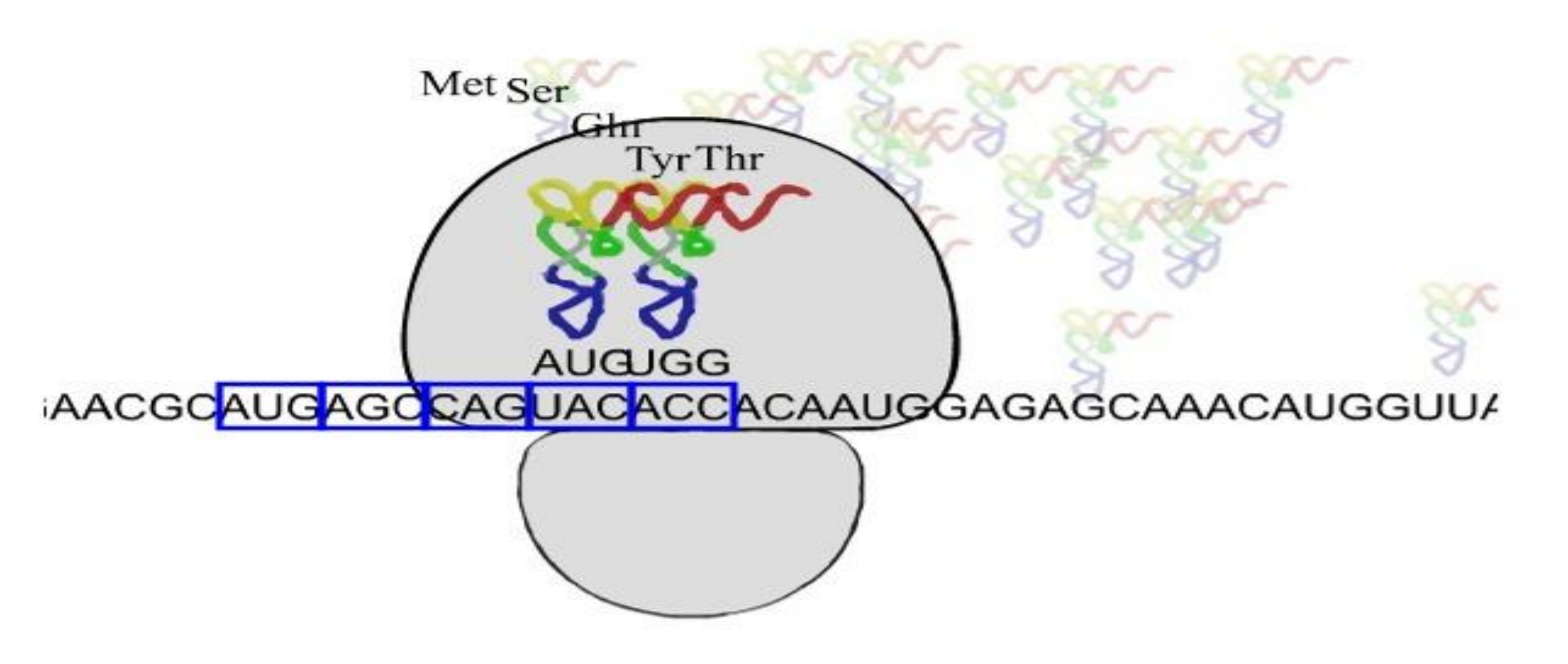
Central Dogma of Molecular Biology : Eukaryotic Model



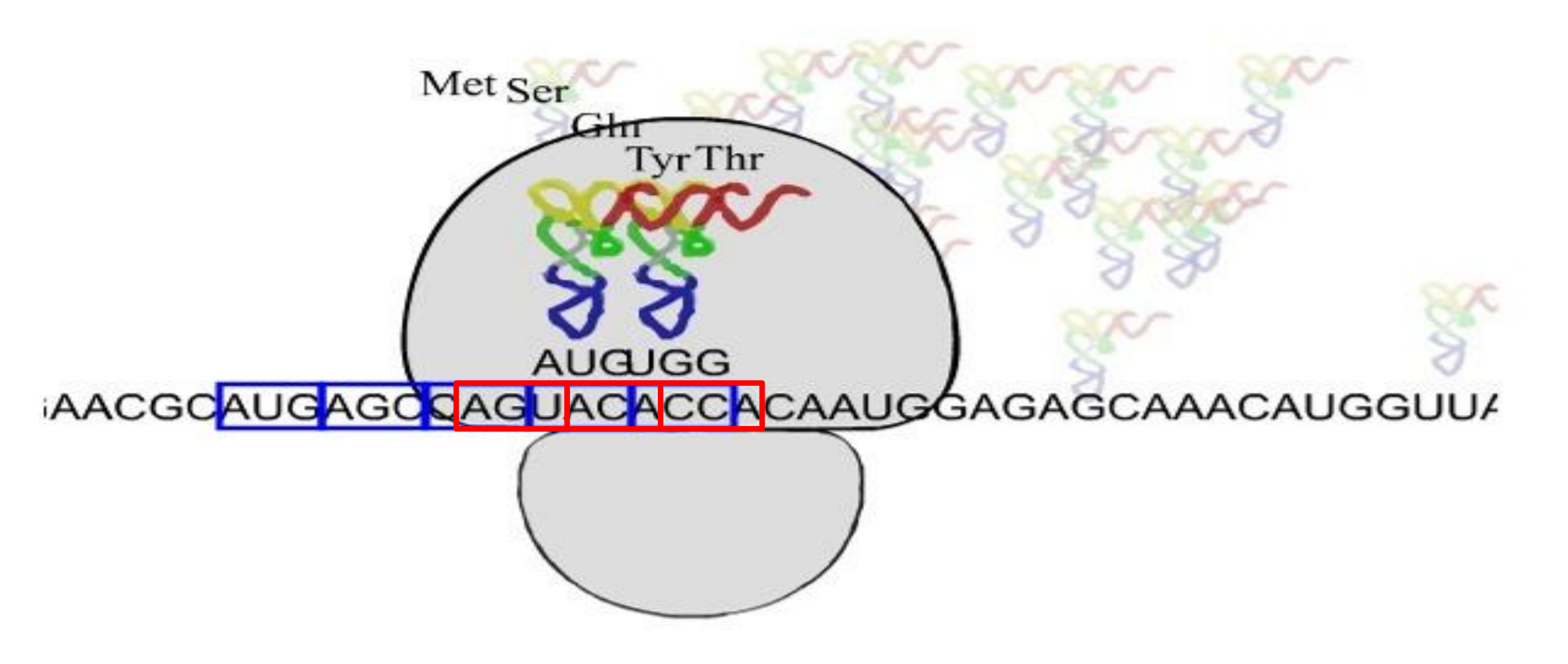
Major errors in translation



Translation



Alternate reading frames lead to gibberish



This gibberish produces a lot of epitopes targeted by the immune system

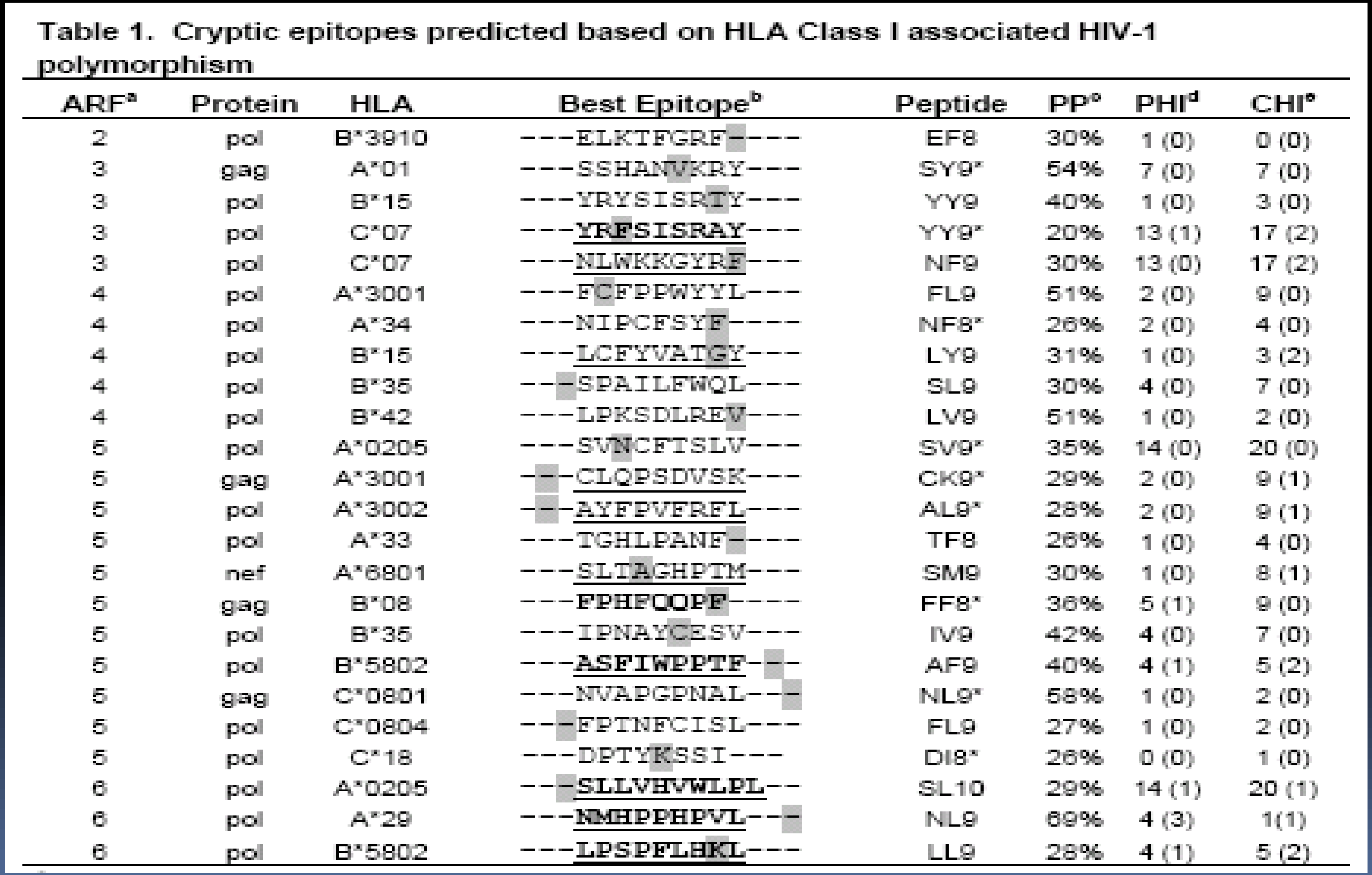


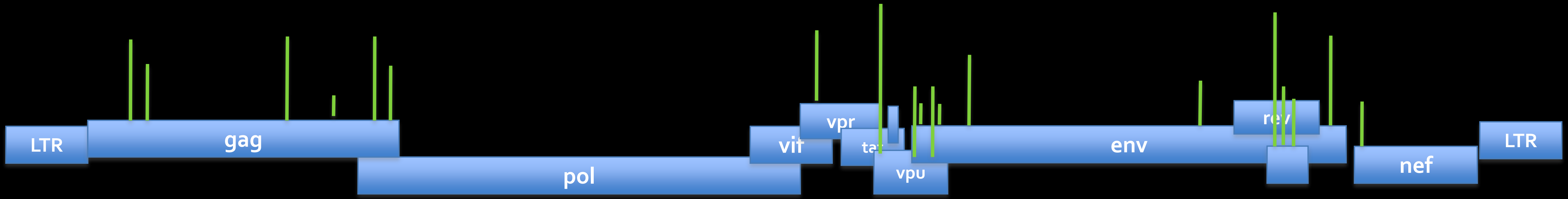
Table 1. Cryptic epitopes predicted based on HLA Class I associated HIV-1 polymorphism

ARF[a]	Protein	HLA	Best Epitope[b]	Peptide	PP[c]	PHI[d]	CHI[e]
2	pol	B*3910	---ELKTFGRF----	EF8	30%	1 (0)	0 (0)
3	gag	A*01	---SSHANVKRY---	SY9*	54%	7 (0)	7 (0)
3	pol	B*15	---YRYSISRTY---	YY9	40%	1 (0)	3 (0)
3	pol	C*07	---YRFSISRAY---	YY9*	20%	13 (1)	17 (2)
3	pol	C*07	---NLWKKGYRF---	NF9	30%	13 (0)	17 (2)
4	pol	A*3001	---FCFPPWYYL---	FL9	51%	2 (0)	9 (0)
4	pol	A*34	---NIPCFSYF----	NF8*	26%	2 (0)	4 (0)
4	pol	B*15	---LCFYVATGY---	LY9	31%	1 (0)	3 (2)
4	pol	B*35	---SPAILFWQL---	SL9	30%	4 (0)	7 (0)
4	pol	B*42	---LPKSDLREV---	LV9	51%	1 (0)	2 (0)
5	pol	A*0205	---SVNCFTSLV---	SV9*	35%	14 (0)	20 (0)
5	gag	A*3001	---CLQPSDVSK---	CK9*	29%	2 (0)	9 (1)
5	pol	A*3002	---AYFPVFRFL---	AL9*	28%	2 (0)	9 (1)
5	pol	A*33	---TGHLPANF----	TF8	26%	1 (0)	4 (0)
5	nef	A*6801	---SLTAGHPTM---	SM9	30%	1 (0)	8 (1)
5	gag	B*08	---FPHFQQPF----	FF8*	36%	5 (1)	9 (0)
5	pol	B*35	---IPNAYCESV---	IV9	42%	4 (0)	7 (0)
5	pol	B*5802	---ASFIWPPTF---	AF9	40%	4 (1)	5 (2)
5	gag	C*0801	---NVAPGPNAL---	NL9*	58%	1 (0)	2 (0)
5	pol	C*0804	---FPTNFCISL---	FL9	27%	1 (0)	2 (0)
5	pol	C*18	---DPTYKSSI---	DI8*	26%	0 (0)	1 (0)
6	pol	A*0205	---SLLVHVWLPL--	SL10	29%	14 (1)	20 (1)
6	pol	A*29	---NMHPPHPVL---	NL9	69%	4 (3)	1(1)
6	pol	B*5802	---LPSPFLHKL---	LL9	28%	4 (1)	5 (2)

Bansal, *J. Exp. Med.*, 2010

Berger, *J. Exp. Med.*, 2010

First evidence that innate arm of immune system drives HIV evolution



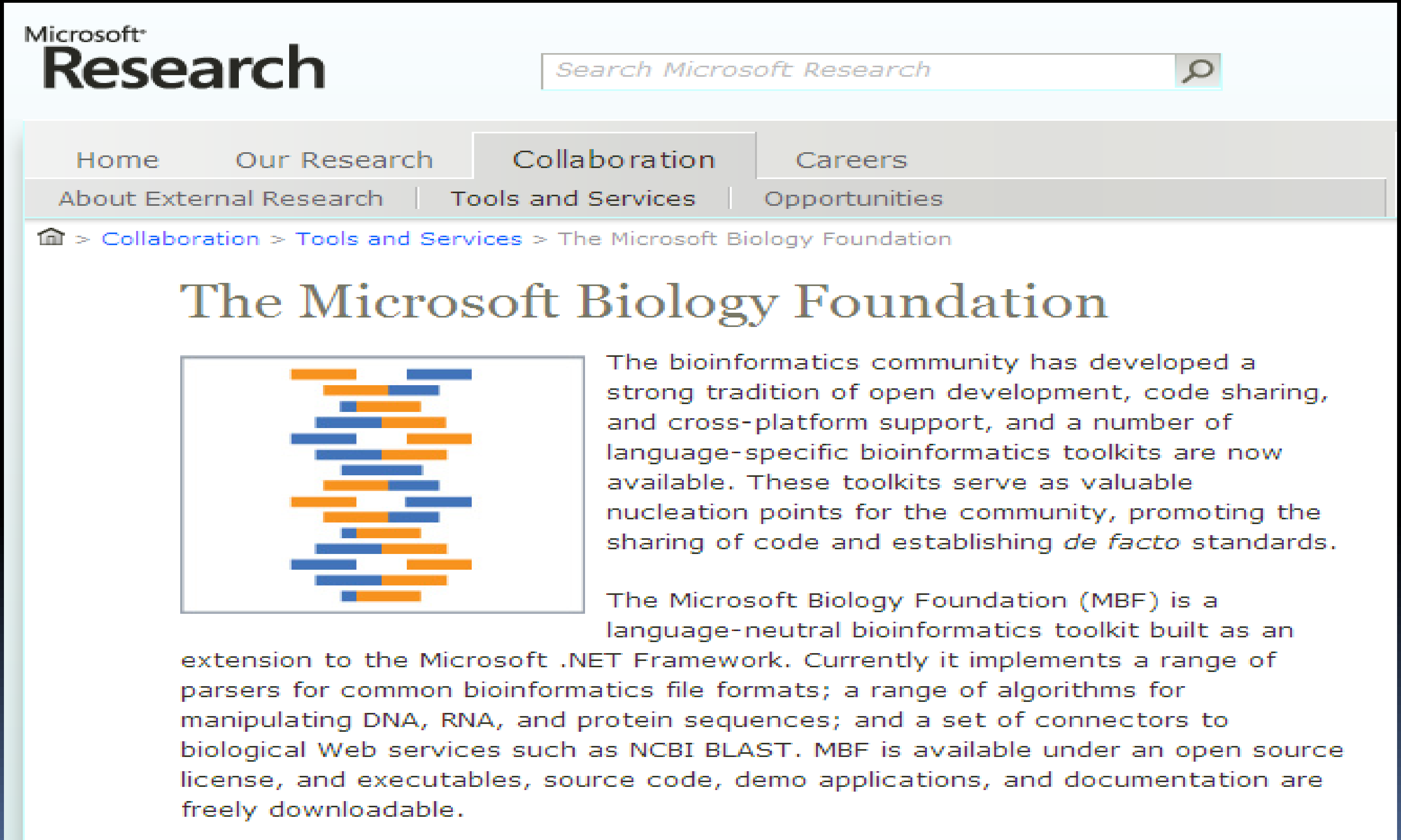
Points of attack by natural killer cells

Summary and next steps

- HIV is not invulnerable
- We can use machine learning and HPC to find HIV’s Achilles’ heel(s)

- Test the vaccine (with Jim Mullins)

PhyloD.net is part of Microsoft Biology Foundation



The Microsoft Biology Foundation

The bioinformatics community has developed a strong tradition of open development, code sharing, and cross-platform support, and a number of language-specific bioinformatics toolkits are now available. These toolkits serve as valuable nucleation points for the community, promoting the sharing of code and establishing *de facto* standards.

The Microsoft Biology Foundation (MBF) is a language-neutral bioinformatics toolkit built as an extension to the Microsoft .NET Framework. Currently it implements a range of parsers for common bioinformatics file formats; a range of algorithms for manipulating DNA, RNA, and protein sequences; and a set of connectors to biological Web services such as NCBI BLAST. MBF is available under an open source license, and executables, source code, demo applications, and documentation are freely downloadable.

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